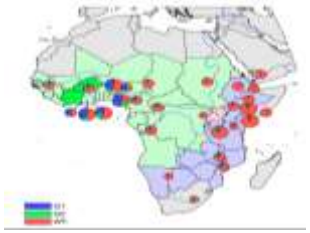
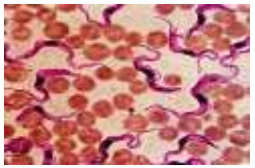
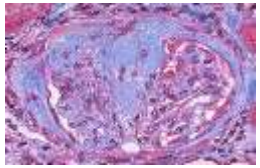
APOL1 associated kidney diseases : Therapeutic Perspectives

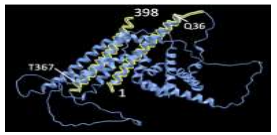
ANJH 2024

B Knebelmann MD, PhD
Department of Adult Nephrology
Reference Center for Hereditary Kidney Diseases (MARHEA)
ERKNet Center
Necker Hospital
bertrand.knebelmann@aphp.fr
Université Paris Cité

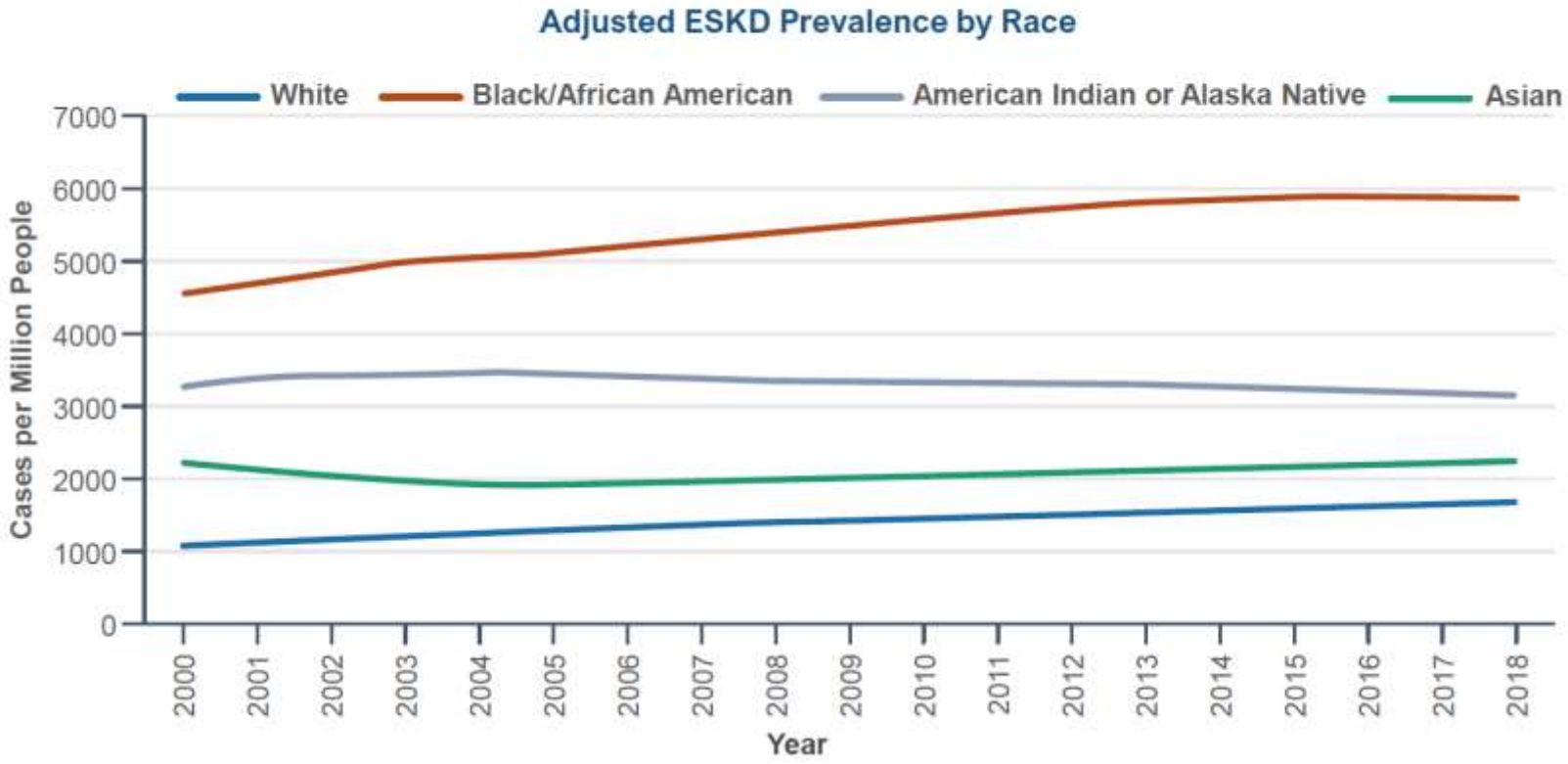




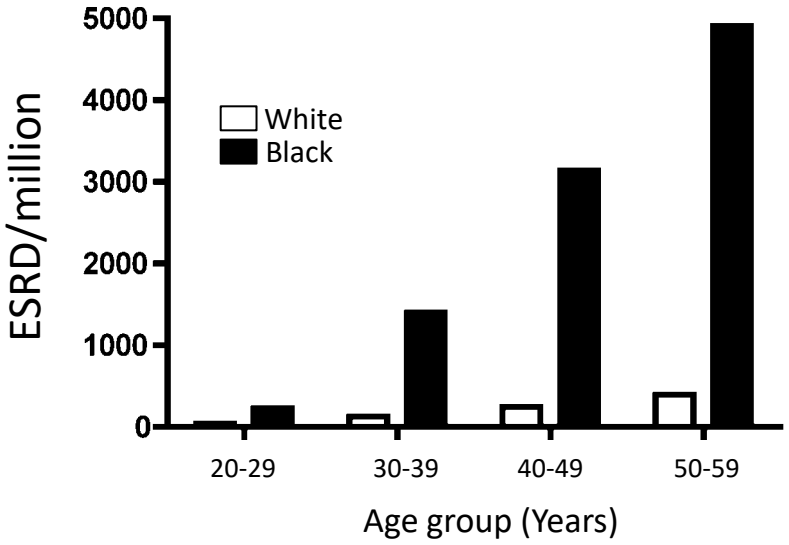




Burden of End-Stage Kidney Disease



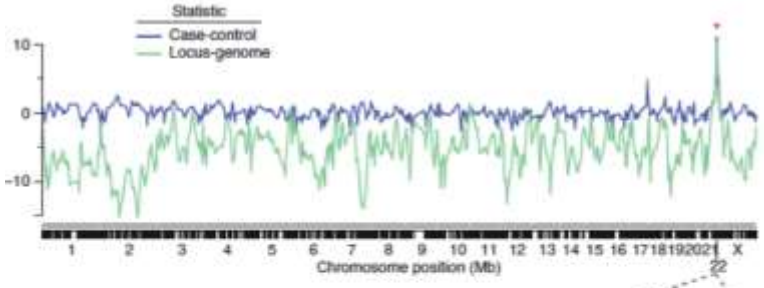
Kidney disease in male Black Americans



Hypertension-attributable ESRD

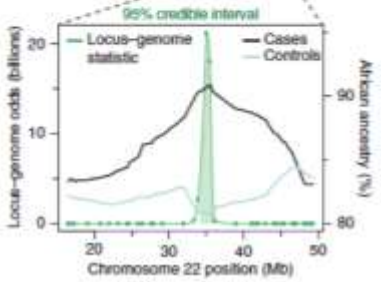
ESRD, end-stage renal disease
United States Renal Data System (USRDS). https://adr.usrds.org/2020/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities. Last accessed April 2022

Discovery of the chromosome 22 locus and APOL1 risk variants



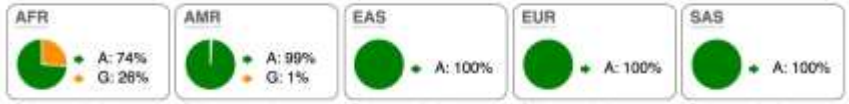
Locus-genome lod score

	Genome-wide	Peak
Initial screen	9.2	12.4
Even markers	8.7	10.1
Odd markers	7.7	8.8
Dense markers at peak	10.5	13.7



Identification of APOL1 risk variants

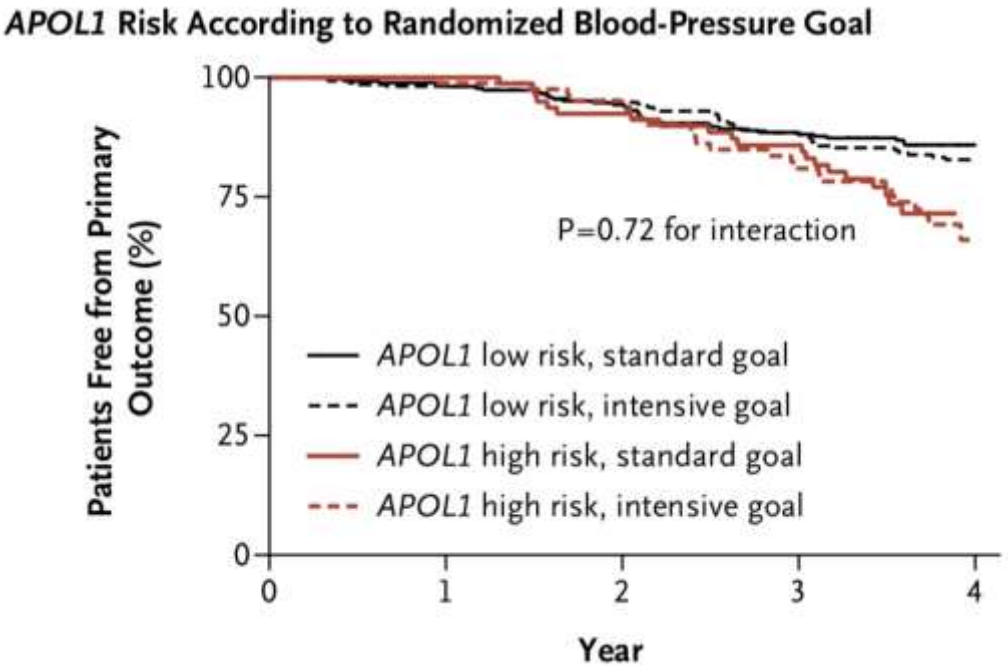
- Two risk variants (G1 and G2)
- Strong association with FSGS
- Strong association with H-ESRD



FSGS, focal segmental glomerulosclerosis; H-ESRD, hypertension-attributed end-stage renal disease

Kopp JB, et al. *Nat Genet*. 2008;40(10):1175–84; Genovese G, et al. *Science*. 2010;329(5993):841–5

Is hypertension a cause or a consequence of 'hypertensive' kidney disease?



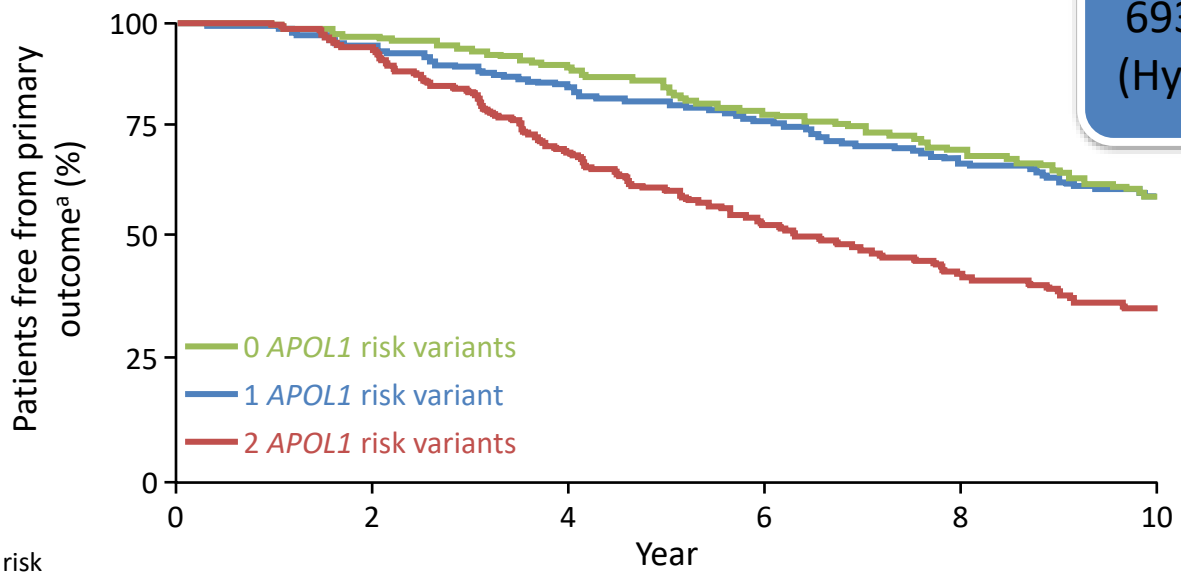
AASK study

AASK, African American Study of Kidney Disease and Hypertension; FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus

Parsa A, et al. *NEJM*. 2013;369(23):2183–96

Renal function decline is more rapid in patients with the *APOL1* high-risk genotype versus those with low-risk genotype

693 patients from AASK study (Hypertension-attributed CKD)



No. at risk						
0 *APOL1* variants	234	225	208	177	146	80
1 *APOL1* variant	299	283	254	223	179	111
2 *APOL1* variants	160	151	114	85	61	30

Parsa A, et al. *N Engl J Med*. 2013;369:2183-2196.

APOL1 Variations in Patients with Steroid-Resistant Nephrotic Syndrome (SRNS) and/or FSGS

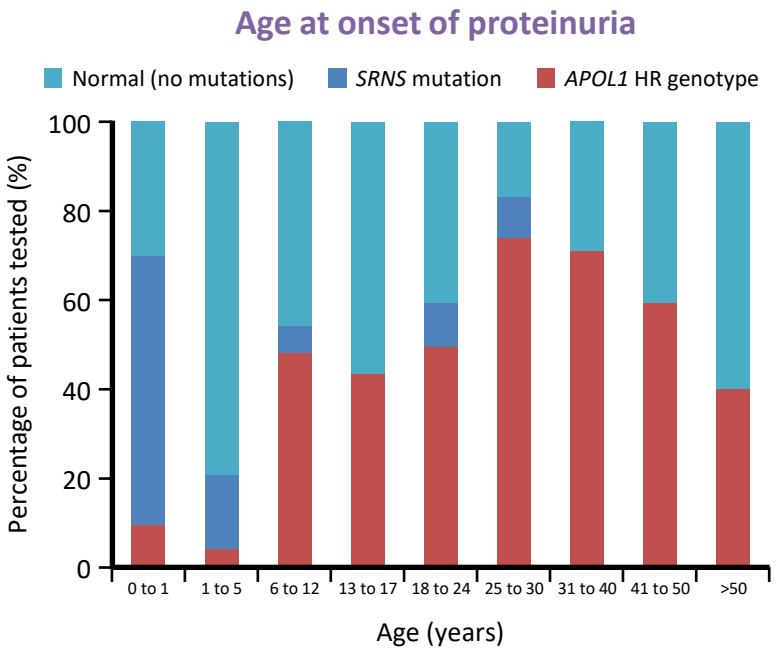
French multicenter cohort of patients with West Indies, French Guyana, or African ancestry

152 patients
- Mean onset of SRNS or FSGS was 17.1 years
- 41 familial cases (26.8%) in 28 families

Sanger (*APOL1*) + NGS targeted gene panel covering 35 SRNS genes

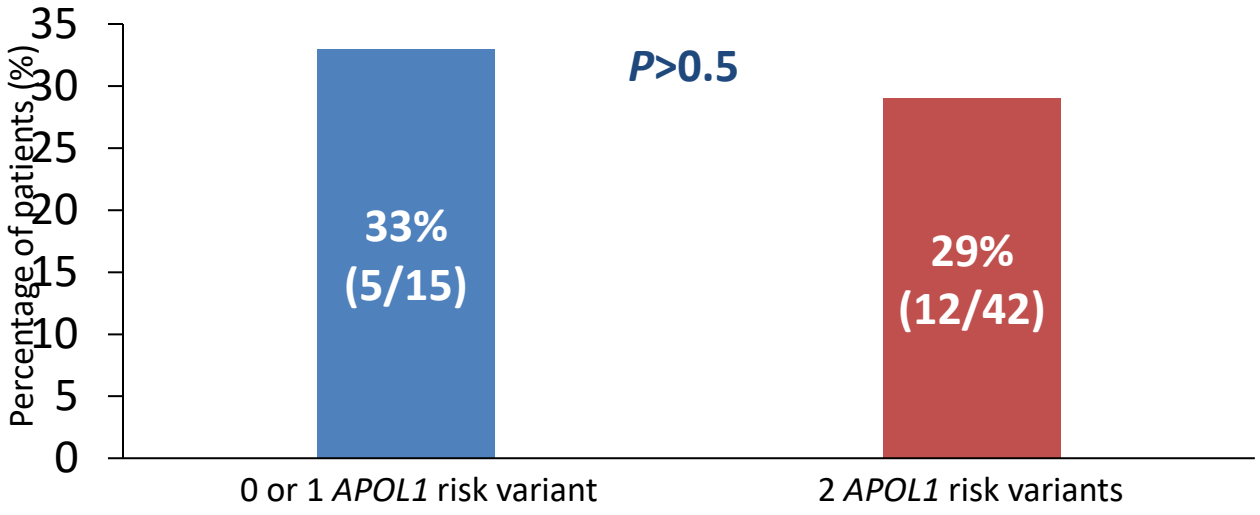
66 (43.1%) patients with *APOL1* high-risk genotype
- 60% (45/75) of patients from the French West Indies
- 27.3% (21/77) of patients originating from Africa
- 41.5% of patients had familial nephropathy

***SRNS* mutations**:
- 1 patient with *APOL1* high-risk genotype (congenital NS)
- 16 patients with *APOL1* low-risk genotype



Gribouval O, et al. *Nephrol Dial Transplant*. 2019;34:1885-1893.

In African American pts with FSGS, steroid sensitivity is similarly low in those with *APOL1* high-risk or low-risk genotypes



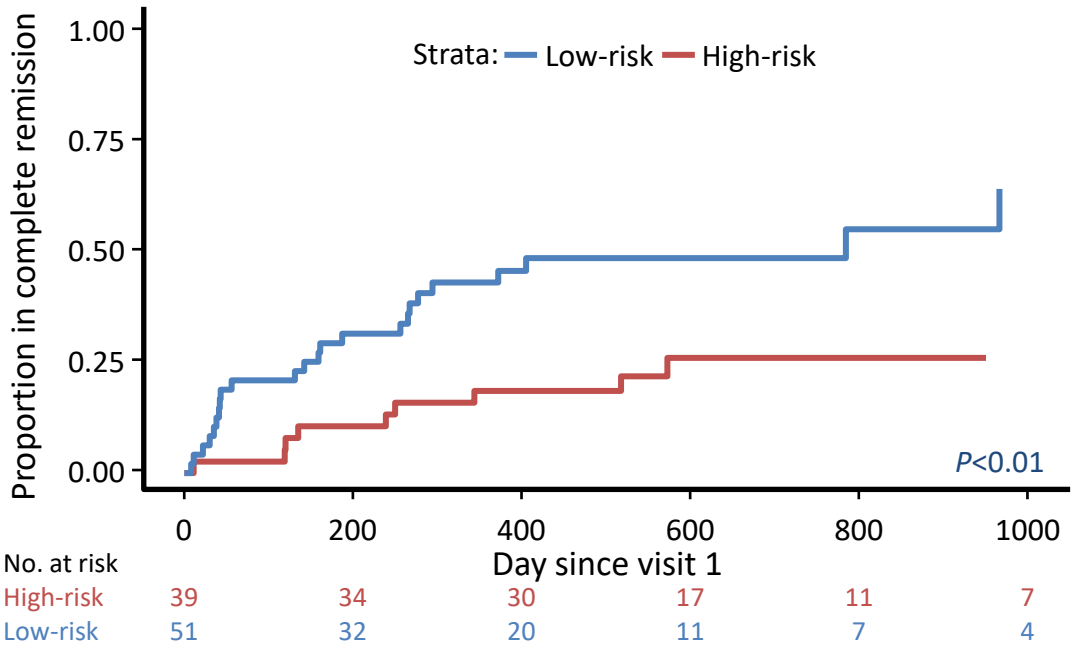
NIH FSGS Genetic Study in the USA

[a]Steroid sensitivity was defined as complete or partial remission in subjects who had received at least 8 week of daily or alternate-day steroid therapy.
APOL1, apolipoprotein L1; FSGS, focal segmental glomerulosclerosis; NIH, National Institutes of Health
Kopp JB, et al. *J Am Soc Nephrol*. 2011;22:2129-2137.

APOL1 risk variants are associated with a decreased kidney disease remission: exploratory analysis from the NEPTUNE study

90 subjects with self-reported Black ancestry
and proteinuria ≥0.5 g/d
FSGS, MCD, and MN
enrolled at first biopsy for primary nephrotic syndrome

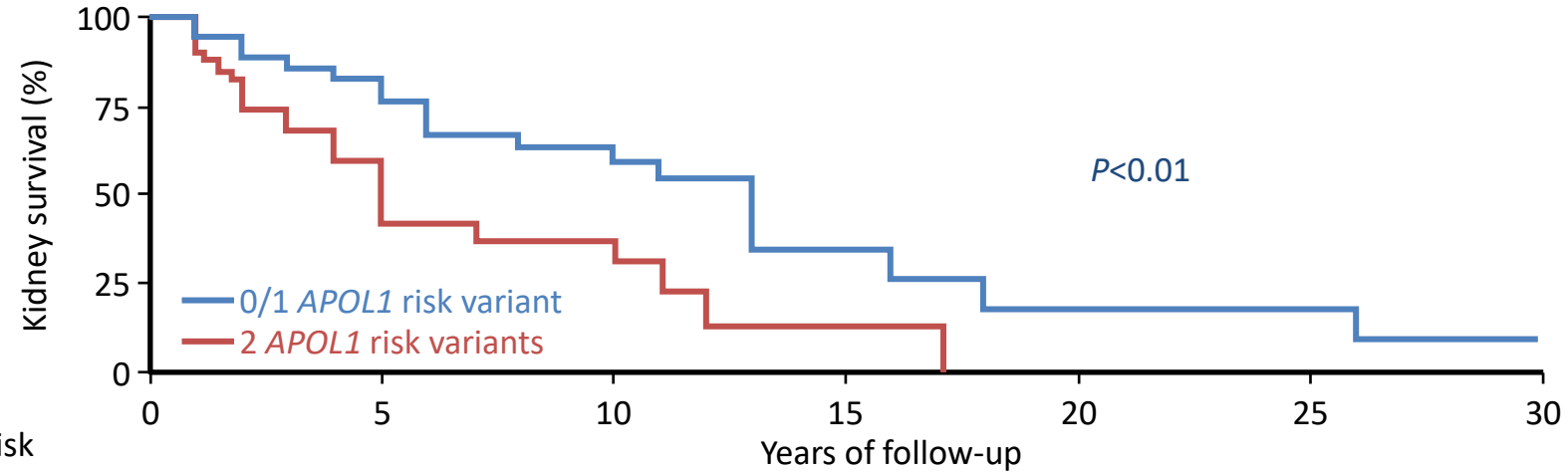
- *APOL1* high-risk genotype was significantly associated with **~70% reduction** in the probability of complete remission at any time, independent of histologic diagnosis



- NEPTUNE study is a prospective, observational study that enrolls children and adults with FSGS, MCD, and MN; the primary outcome was a composite measure of change in urinary protein excretion and change in renal function.

Sampson MG, et al. *J Am Soc Nephrol*. 2016;27:814-823; NEPTUNE. https://repository.niddk.nih.gov/studies/neptune/. Accessed April 2022.

TWO *APOL1* risk variants are associated with reduced kidney survival in patients with FSGS

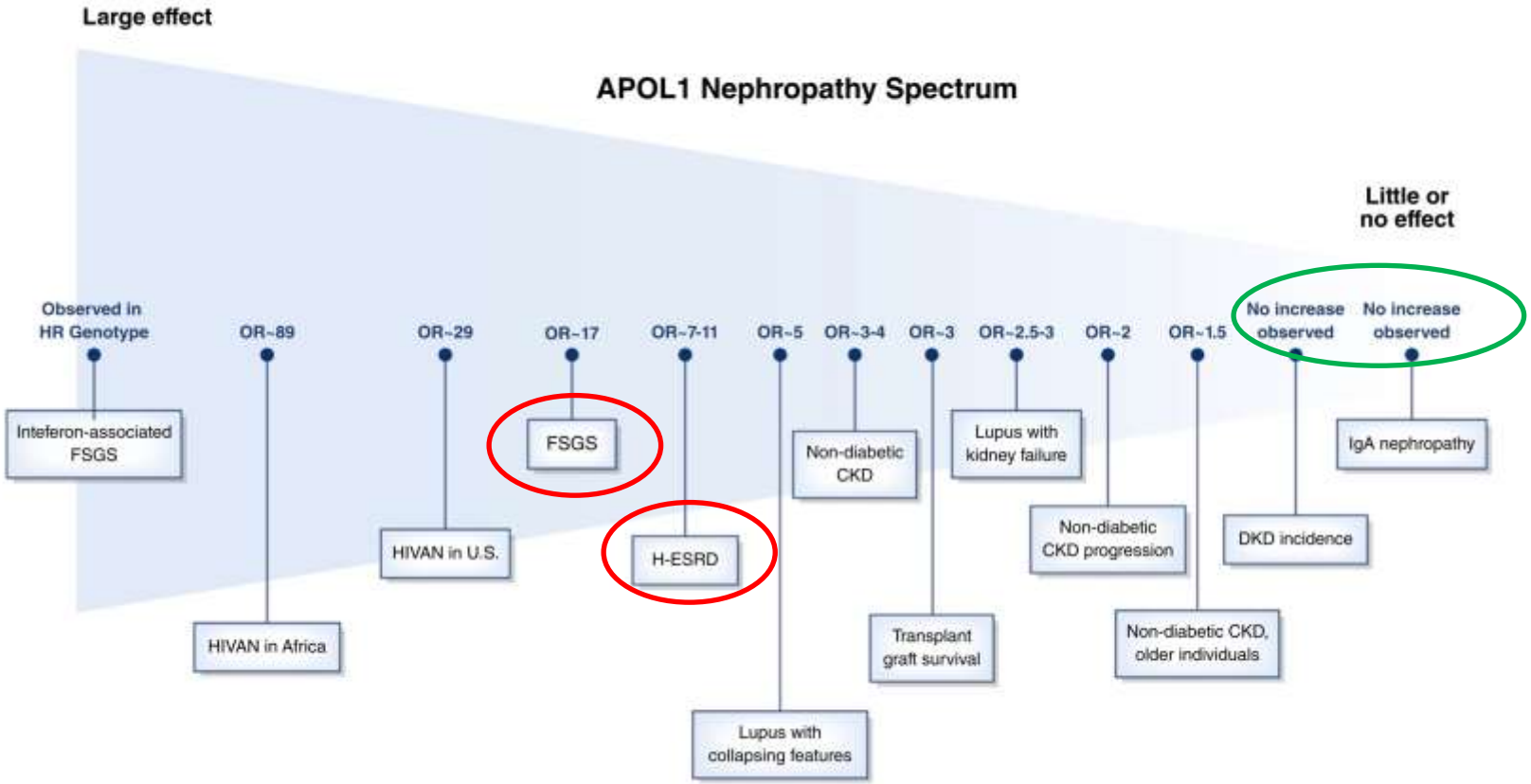


No. at risk				
0/1 variant	34	24	12	4
2 variants	58	19	11	1

Kidney survival in 92 African American patients with primary FSGS
NIH FSGS Genetic Study

Kopp JB, et al. *J Am Soc Nephrol*. 2011;22:2129-2137.

APOL1 Mediated Kidney Disease (AMKD): one gene, many diseases

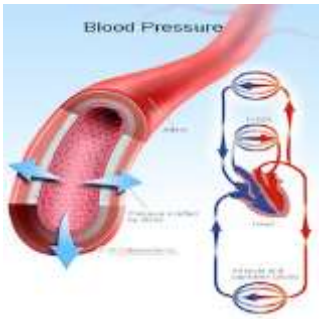


Friedman DJ and Pollak MR. *CJASN*. 2021;16(2):294–303

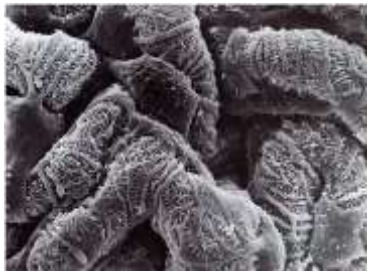
Same variants, different phenotypes

APOL1

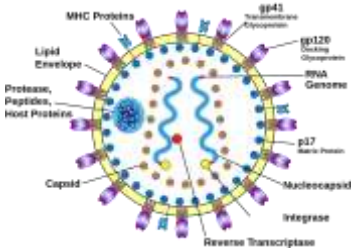
Hypertensive kidney disease
7-10-fold increased risk
(vascular)



FSGS
~15-20-fold increased risk
(primary glomerular)

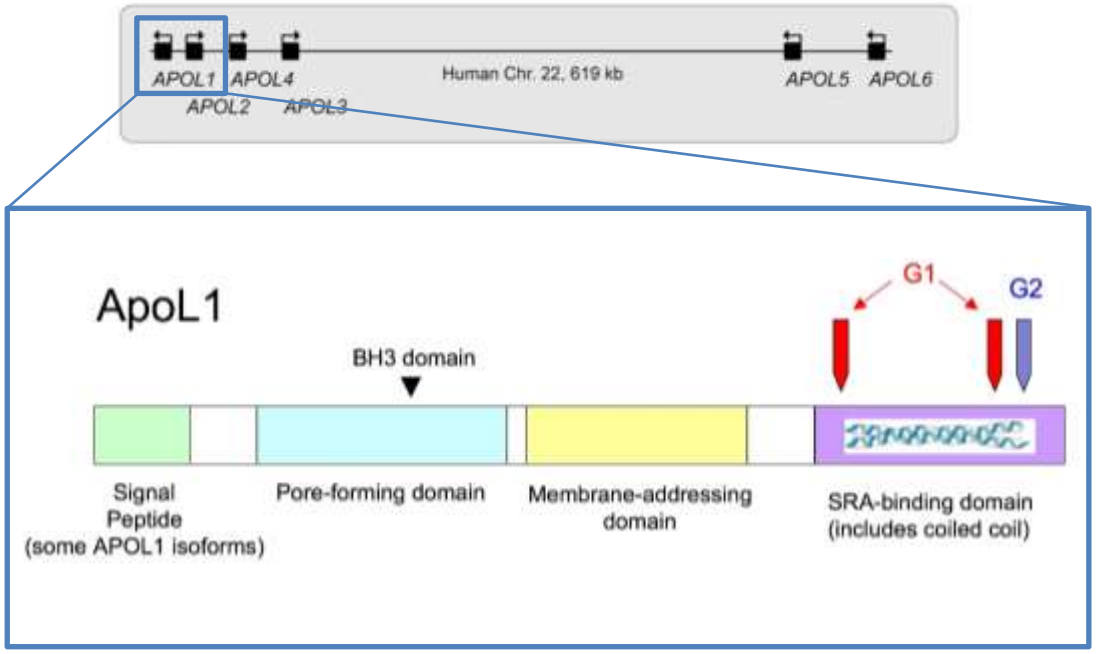


HIV nephropathy
30-90-fold increased risk
(infectious)



FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus

APOL1 basics

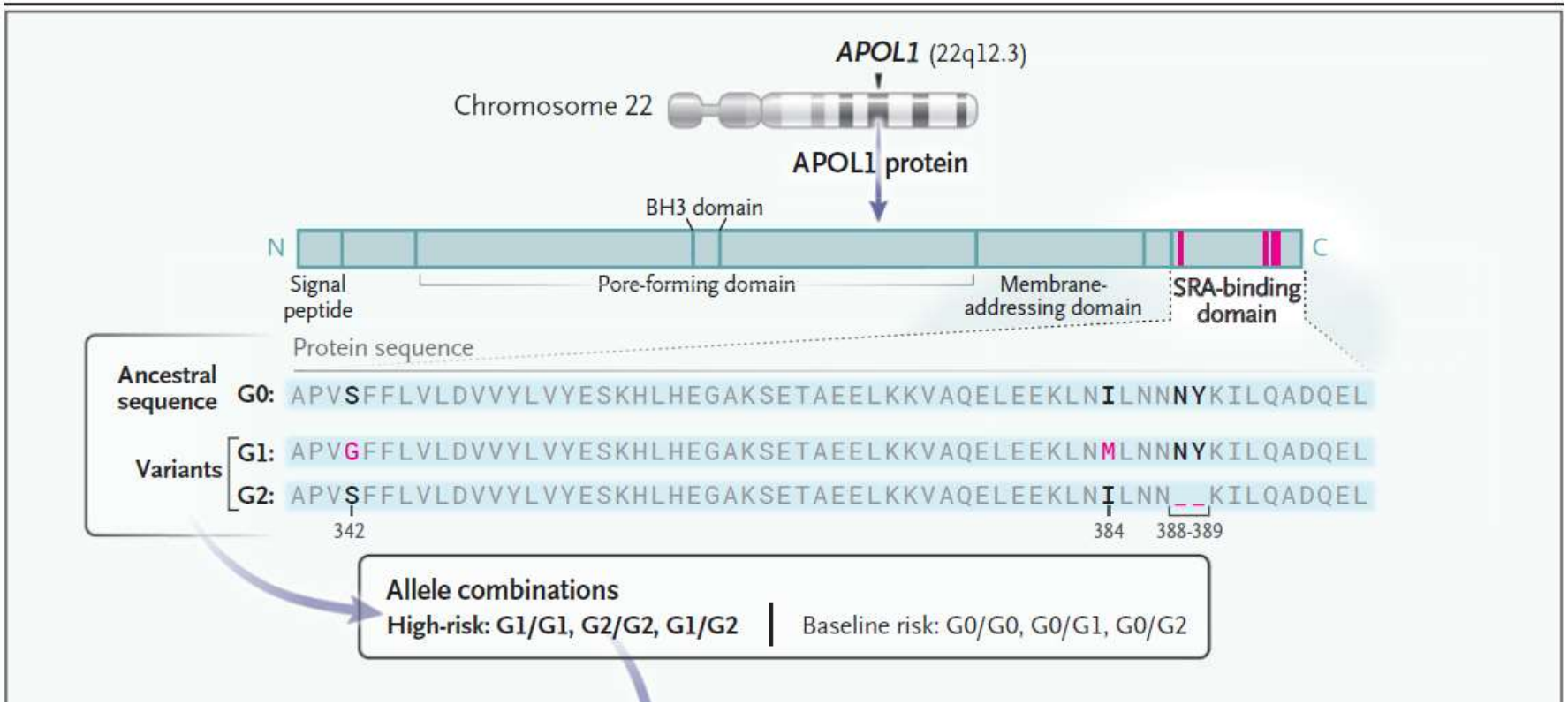


- Circulates on HDL3
- Expressed in many tissues, especially blood vessels
- In the kidney, protein found primarily in podocytes and the microvasculature

BCL-2, B-cell lymphoma 2; BH3, bcl-2 Homology 3; Chr, chromosome; HDL3, high-density lipoprotein 3; SRA, serum resistance antigen

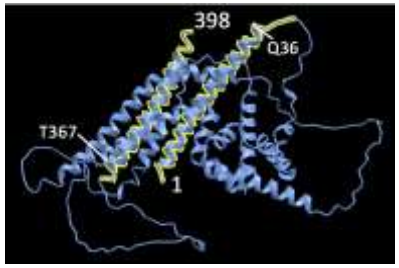
Smith EE and Malik HS. *Genome Res*. 2009;19(5):850–8; Friedman DJ and Pollak MR. *Annu Rev Physiol*. 2020;82:323–42

High Risk ApoL1 genotypes



Williams WW, IngelfingerJ, N engl j med 388;11 nejm.org March 16, 2023

APOL1 HR frequency



- 50–60% of African Americans have at least one copy of G1 and/or G2
- Recessive mode of inheritance
- 12–15% of African Americans (4–5 million individuals) are high-risk homozygotes (HR)
- Variants nearly absent in European Americans
- Unusually large effect size for common variants

NEN study : intermediate analysis:
Prevalence of HR genotype in FSGS and NDKD

MANY PARTICIPANTS HAVE TWO *APOL1* VARIANTS

Table 2. Percent of Participants with 2, 1, or 0 *APOL1* Variants

Number of *APOL1* variants, n (%)	FSGS N = 511	Proteinuric NDKD N = 1395	Total N = 1906
2 *APOL1* variants[a]	215 (42.1)	289 (20.7)	504 (26.4)
1 *APOL1* variant[b]	107 (20.9)	419 (30.0)	526 (27.6)
0 *APOL1* variants[c]	189 (37.0)	687 (49.2)	876 (46.0)

Table 3. Summary of *APOL1* Genotypes

APOL1 genotype, n (%)	FSGS N = 511	Proteinuric NDKD N = 1395	Total N = 1906
2 *APOL1* variants			
G1/G1	107 (20.9)	139 (10.0)	246 (12.9)
G1/G2	86 (16.8)	122 (8.7)	208 (10.9)
G2/G2	22 (4.3)	28 (2.0)	50 (2.6)

Kate Bramham et al, ASN Kidney Week, Philadelphia, PA, USA, November 1-5, 2023

Table 5. Summary of Participants with Two *APOL1* Variants by Country or Region

G1/G1, G1/G2, or *G2/G2 APOL1* genotype by region or country	FSGS N = 511 n/N' (%)	Proteinuric NDKD N = 1395 n/N' (%)	Total N = 1906 n/N' (%)
North America			
United States	127/292 (43.5)	226/1052 (21.5)	353/1344 (26.3)
Europe	73/143 (51.0)	58/190 (30.5)	131/333 (39.3)
United Kingdom	49/79 (62.0)	44/117 (37.6)	93/196 (47.4)
France	23/30 (76.7)	4/28 (14.3)	27/58 (46.6)
Spain	0/22	1/27 (3.7)	1/49 (2.0)
Portugal	1/11 (9.1)	4/11 (36.4)	5/22 (22.7)
Netherlands	0/1	2/4 (50.0)	2/5 (40.0)
Belgium	0	3/3 (100.0)	3/3 (100.0)
South America	15/76 (19.7)	5/153 (3.3)	20/229 (8.7)
Brazil	11/62 (17.7)	3/127 (2.4)	14/189 (7.4)
Colombia	4/14 (28.6)	2/26 (7.7)	6/40 (15.0)

-13% of Black Americans carry two high-risk alleles

- in certain West African populations, the rate of HR genotypes may be as high as 20-25%

-15% of HR *APOL1* genotype will develop ESKD

-5%-8%, will develop FSGS

-13% of Black Americans carry two high-risk alleles

- in certain West African populations, the rate of HR genotypes may be as high as 20-25%

-15% of HR *APOL1* genotype will develop ESKD

-5%-8%, will develop FSGS

Are there genetic modifiers
inluencing the appearance of kidney diseases
in HR Apol1 inividuals?

genetics of kidney disease

Variant upon variant: kidney-disease risk associated with *APOL1 G2* genetic variants is abrogated by the *APOL1* p.N264K variant

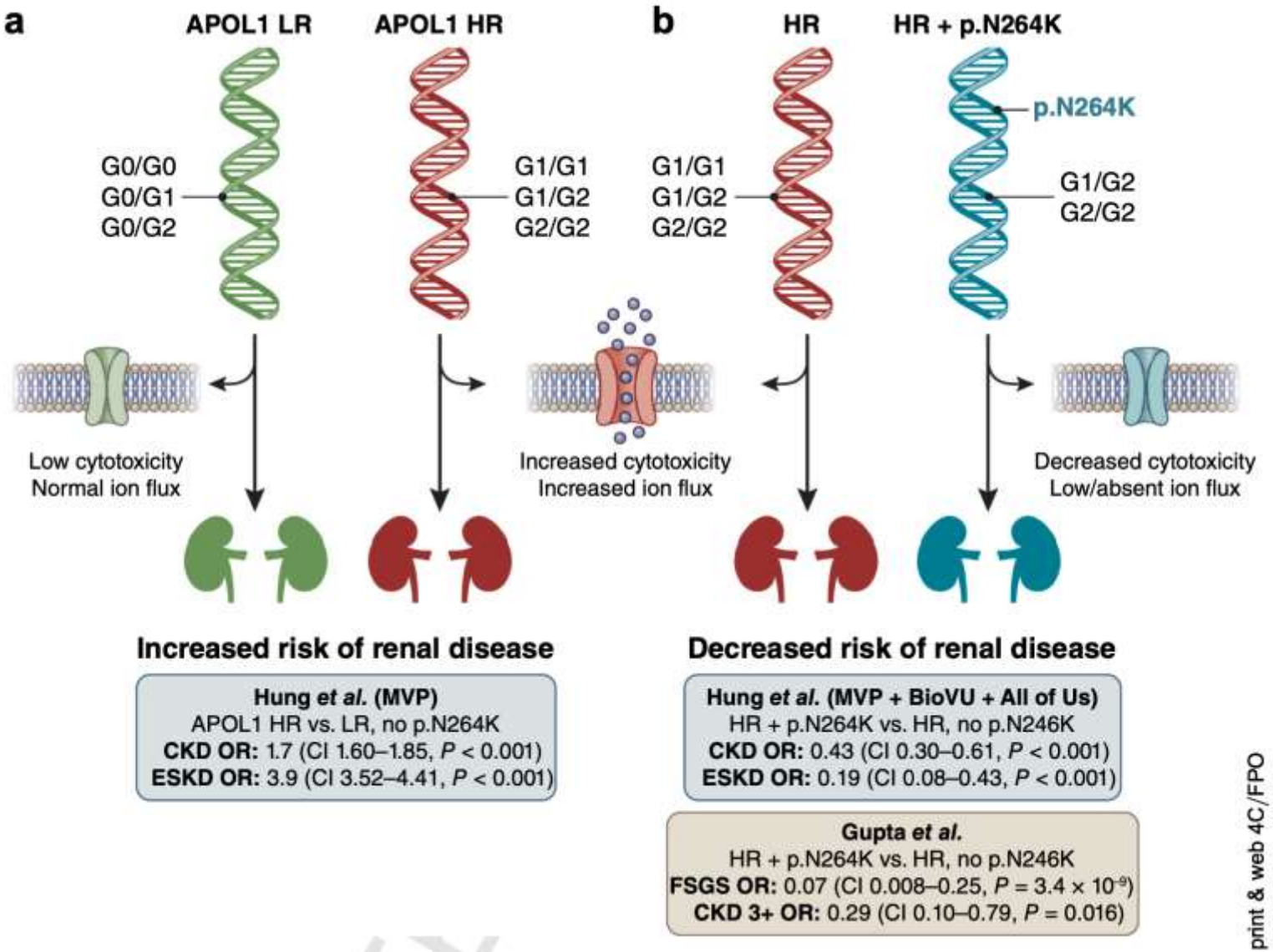
Sethu M. Madhavan[1] and Johannes Schlöndorff[1]

-Million Veteran Program (121,492 participants of African ancestry)
-Vanderbilt University Medical Center Biobank (BioVU),
-National Institutes of Health All of Us Research Program cohorts (Hung et al. ; top box),

(FSGS) case– control cohort and CKD case–control cohort derived from REGARDS (REasons for Geographic and Racial Differences in Stroke) and eMERGE-III (Electronic Medical Records and Genomics Phase III)

Hung, J Am Soc Nephrol. 2023;34:1889–1899; Guptta, Nat Commun. 2023;14:7836.

The APOL1 p.N264K variant in the background of the G2 risk allele reduces the risk of FSGS, CKD and ESKD in individuals w/ APOL1 HR genotypes G1/G2 or G2/G2.



print & web 4C/FPO

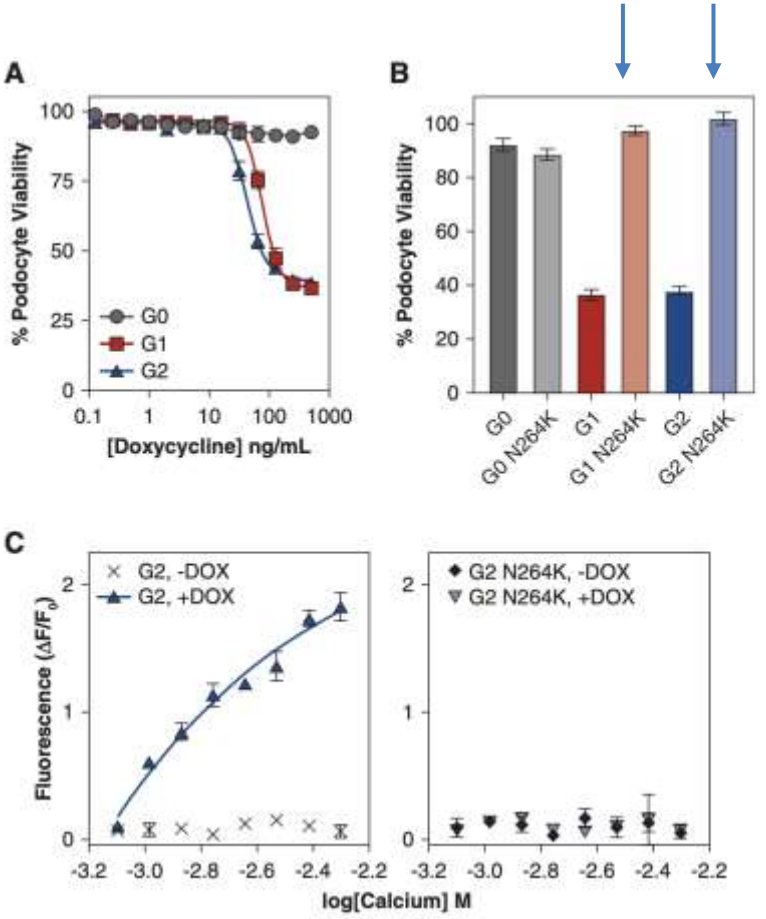
CLINICAL RESEARCH www.jasn.org OPEN

Genetic Inhibition of APOL1 Pore-Forming Function Prevents APOL1-Mediated Kidney Disease

Adriana M. Hung,[1,2] Victoria A. Assimon,[3] Hua-Chang Chen,[1,4] Zhihong Yu,[1,4] Caitlyn Vlasschaert,[5] Jefferson L. Triozzi,[2] Helen Chan,[3] Lee Wheless,[6] Otis Wilson,[1,2] Shailja C. Shah,[7] Taralynn Mack,[1,8] Trevor Thompson,[2] Michael E. Matheny,[1,4,9] Saranya Chandrasekar,[3] Sahar V. Mozaffari,[3] Cecilia P. Chung,[10] Philip Tsao,[11,12] Katalin Susztak,[13] Edward D. Siew,[1,2] Karol Estrada,[3] J. Michael Gaziano,[14,15] Robert R. Graham,[3] Ran Tao,[1,4] Maarten Hoek,[3] Cassianne Robinson-Cohen,[3] Eric M. Green,[7] and Alexander G. Bick,[8,14] for the Million Veteran Program*

APOL1 variants G1/ G2
are toxic when overexpressed
in human immortalized podocytes
But much less N246K

G2 APOL1-mediated calcium transit is blocked by the N246K mutation in HEK cells.

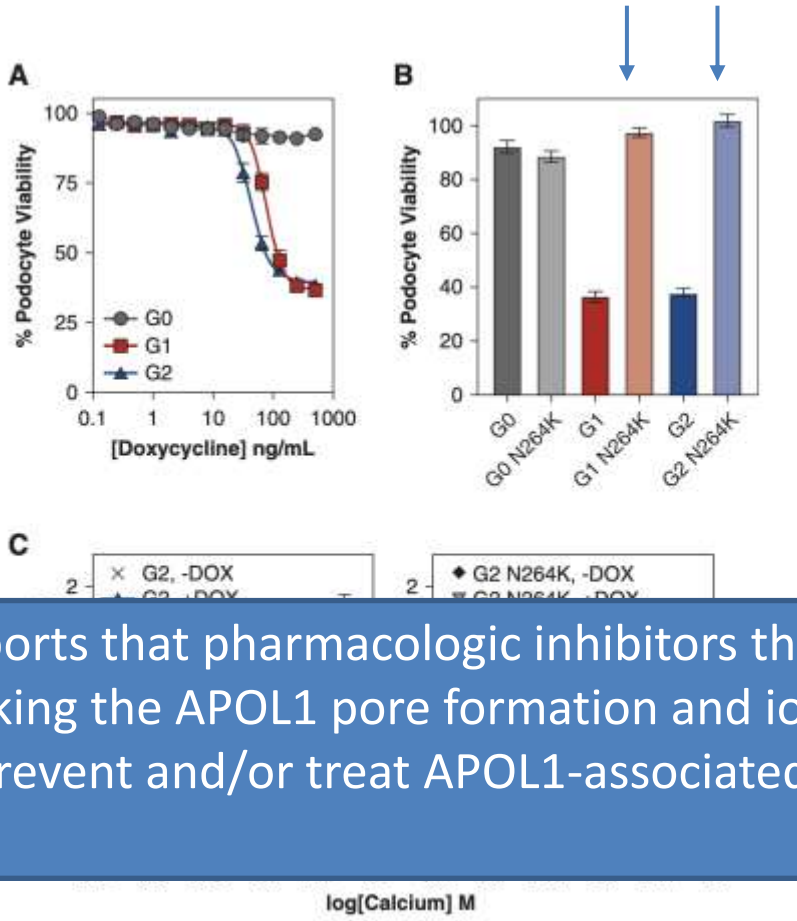


CLINICAL RESEARCH www.jasn.org OPEN

Genetic Inhibition of APOL1 Pore-Forming Function Prevents APOL1-Mediated Kidney Disease

Adriana M. Hung,[1,2] Victoria A. Assimon,[3] Hua-Chang Chen,[1,4] Zhihong Yu,[1,4] Caitlyn Vlasschaert,[5] Jefferson L. Triozzi,[2] Helen Chan,[3] Lee Wheless,[6] Otis Wilson,[1,2] Shailja C. Shah,[7] Taralynn Mack,[1,8] Trevor Thompson,[2] Michael E. Matheny,[1,4,9] Saranya Chandrasekar,[3] Sahar V. Mozaffari,[3] Cecilia P. Chung,[10] Philip Tsao,[11,12] Katalin Susztak,[13] Edward D. Siew,[1,2] Karol Estrada,[3] J. Michael Gaziano,[14,15] Robert R. Graham,[3] Ran Tao,[1,4] Maarten Hoek,[3] Cassianne Robinson-Cohen,[3] Eric M. Green,[7] and Alexander G. Bick,[8,14] for the Million Veteran Program*

APOL1 variants G1/ G2
are toxic when overexpressed
in human immortalized podocytes
But much less N246K

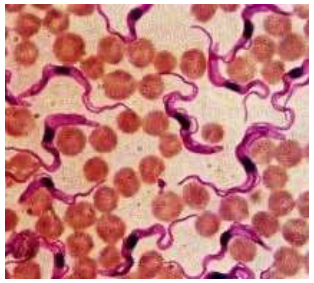


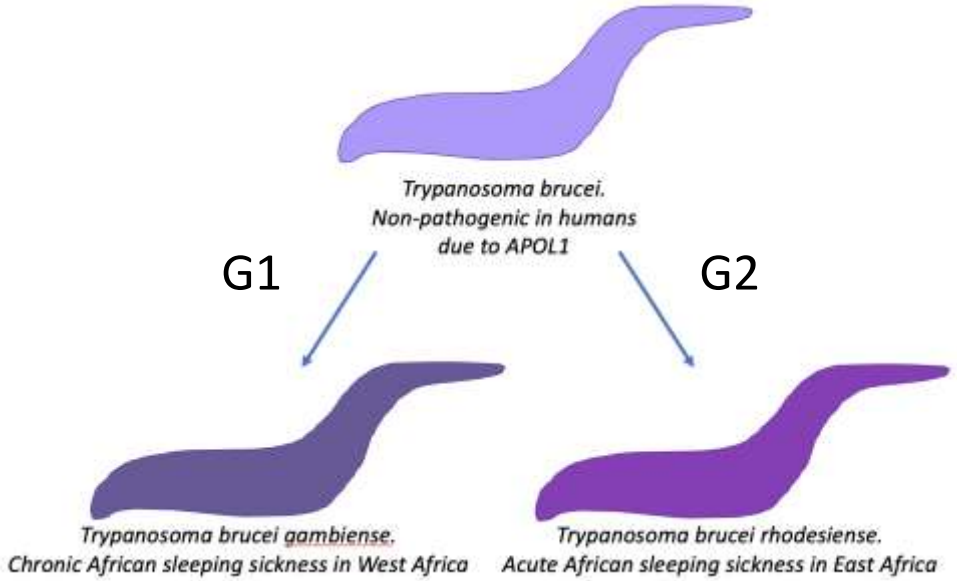
This human genetic observation supports that pharmacologic inhibitors that mimics this genetic mutation by blocking the APOL1 pore formation and ion channel conduction may be able to prevent and/or treat APOL1-associated kidney disease.

5 questions about APOL1 origins and basic biology

- Why are the APOL1 variants restricted to people of recent African Ancestry?
- Why are these highly deleterious variants so common?
- Are APOL1 risk variants loss- or gain-of-function?
- Why do some people with the high-risk genotype get kidney disease while others do not?
- How do APOL1 risk variants injure kidney cells?

Why are these highly deleterious variants so common?



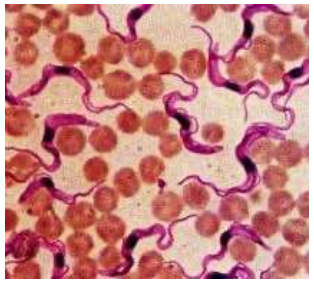


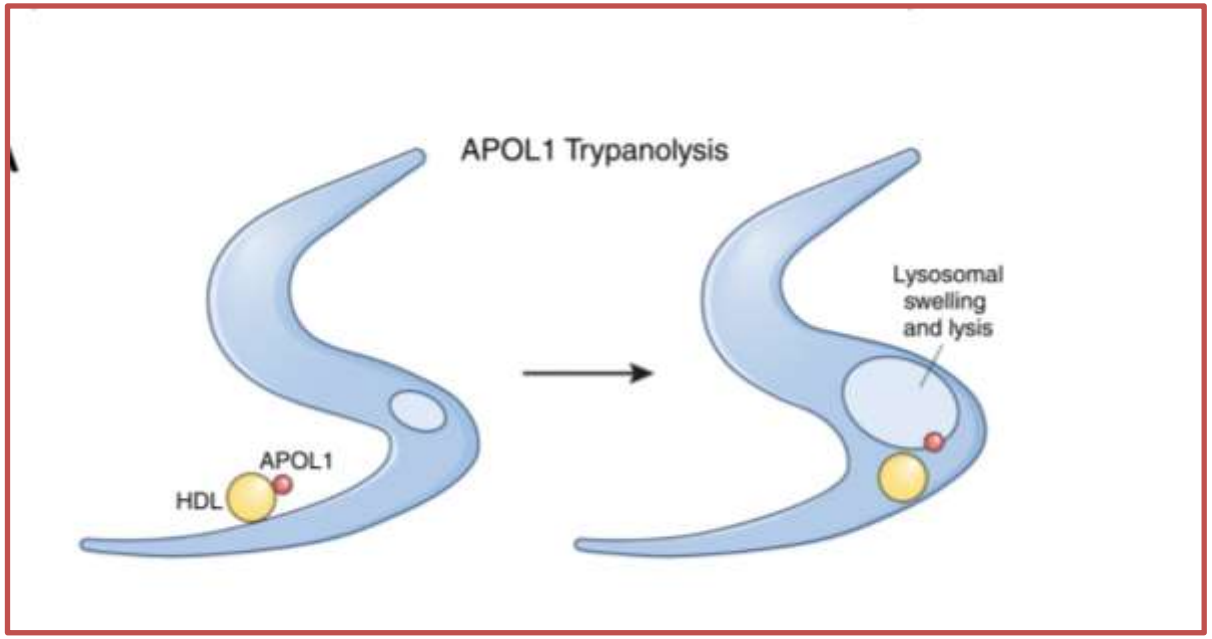
APOL1 risk variants protect against African trypanosomiasis

Friedman DJ and Pollak MR. *Annu Rev Physiol*. 2020;82:323–42

Why are these highly deleterious variants so common?

APOL1 risk variants protect against African trypanosomiasis





Friedman DJ and Pollak MR. *Annu Rev Physiol*. 2020;82:323–42

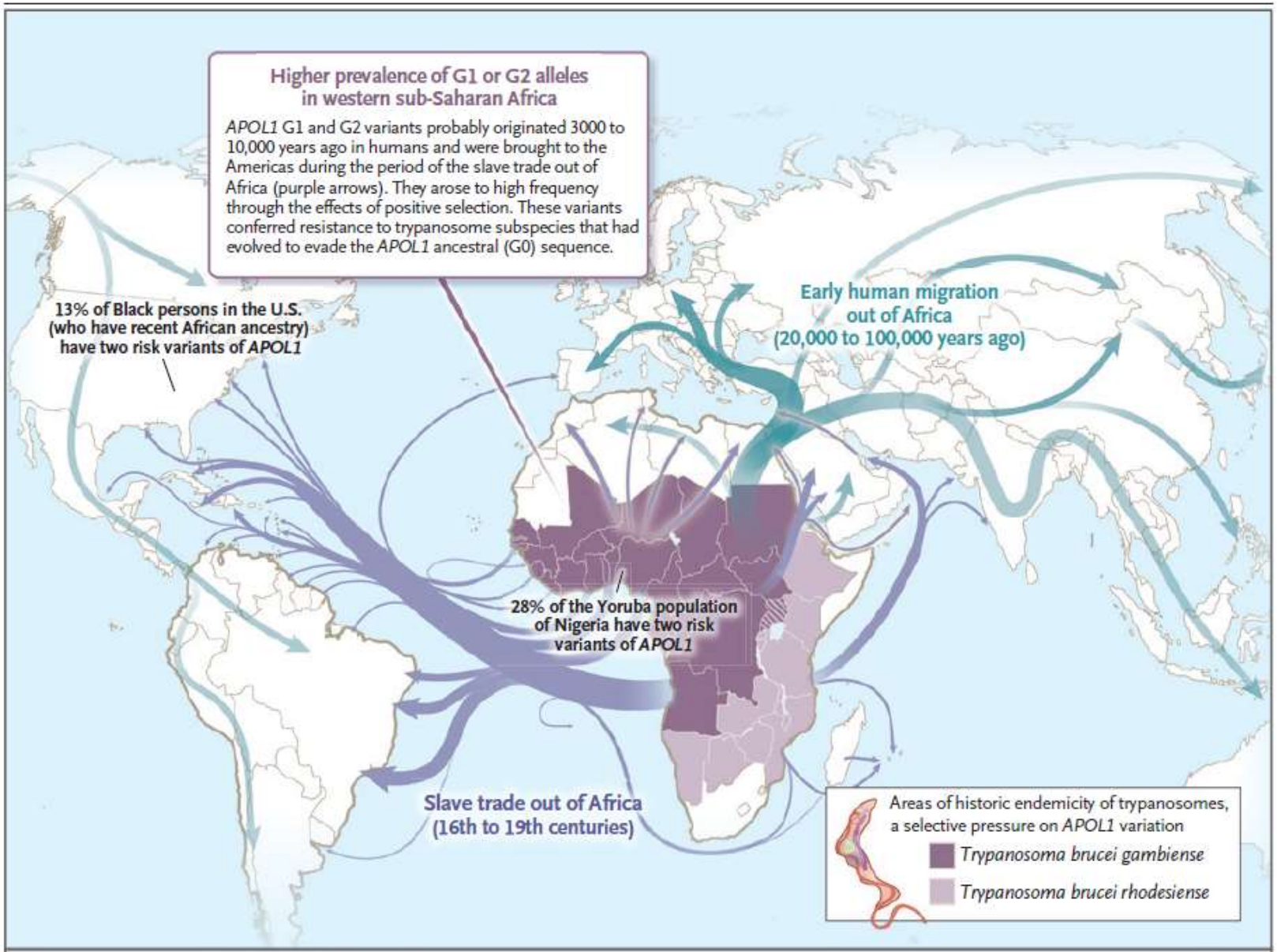
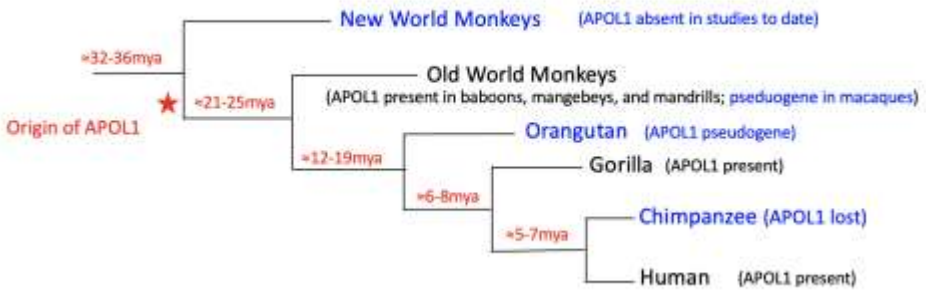
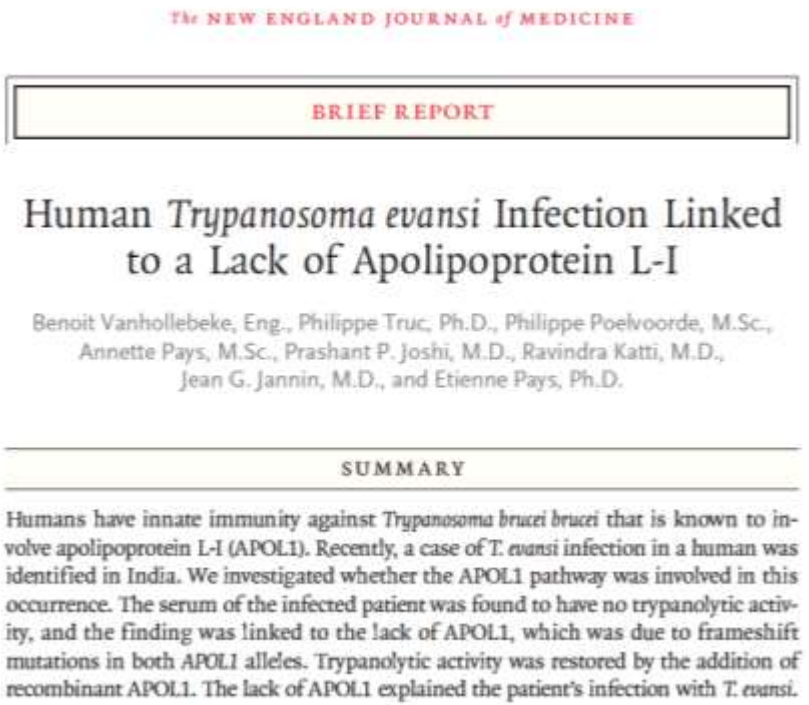


Figure 2. Global Migration and Prevalence of *APOL1* G1 and G2 Variants.

Williams WW, IngelfingerJ, N engl j med 388;11 nejm.org March 16, 2023

Are APOL1 risk variants loss- or gain-of-function?





The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Human *Trypanosoma evansi* Infection Linked to a Lack of Apolipoprotein L-I

Benoit Vanhollebeke, Eng., Philippe Truc, Ph.D., Philippe Poelvoorde, M.Sc., Annette Pays, M.Sc., Prashant P. Joshi, M.D., Ravindra Katti, M.D., Jean G. Jannin, M.D., and Etienne Pays, Ph.D.

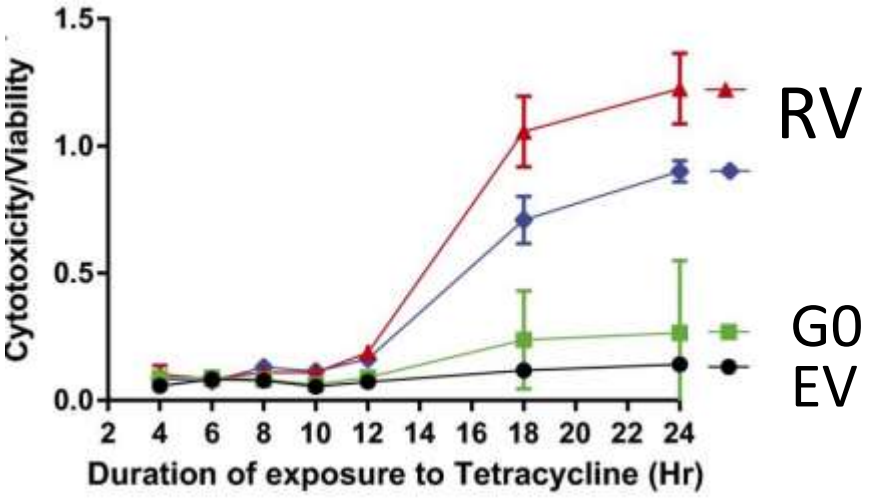
SUMMARY

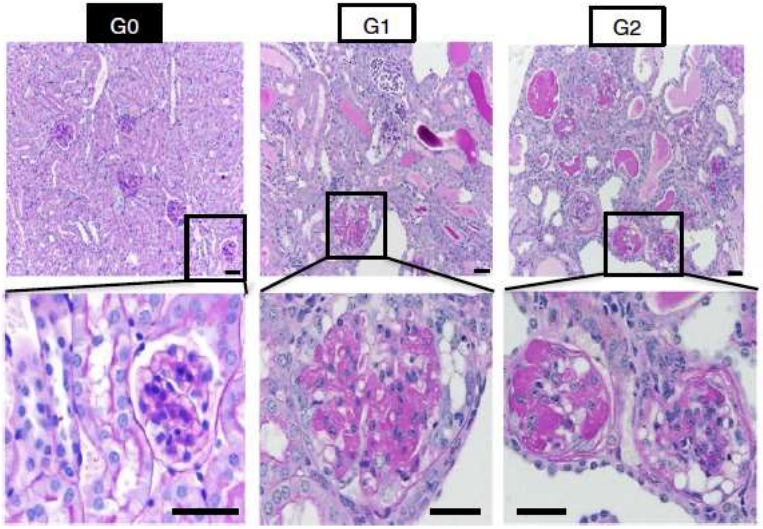
Humans have innate immunity against *Trypanosoma brucei brucei* that is known to involve apolipoprotein L-I (APOL1). Recently, a case of *T. evansi* infection in a human was identified in India. We investigated whether the APOL1 pathway was involved in this occurrence. The serum of the infected patient was found to have no trypanolytic activity, and the finding was linked to the lack of APOL1, which was due to frameshift mutations in both *APOL1* alleles. Trypanolytic activity was restored by the addition of recombinant APOL1. The lack of APOL1 explained the patient's infection with *T. evansi*.

The APOL1 gene exists only in humans and some primates; humans null for APOL1 have normal kidneys ++

Friedman DJ. *Semin Nephrol*. 2017;37(6):508–13; Vanhollebeke B, et al. *N Engl J Med*. 2006;355(26):2752–6

APOL1 risk variants are gain-of-function

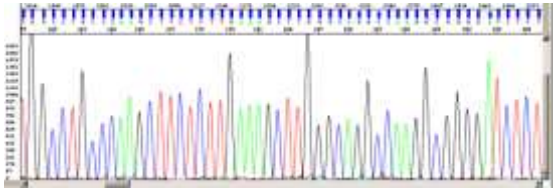




Overexpression of APOL1 RV (but not G0) are toxic in cells and mimics FSGS in mice

Olabisi OA, et al. *Proc Natl Acad Sci U S A*. 2016;113(4):830–7; Beckerman P, et al. *Nat Med*. 2017;23(4):429–8

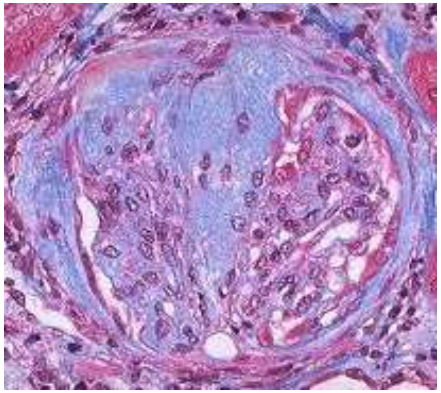
Why do only some people with the APOL1 high-risk genotype get disease?



APOL1 high-risk genotype

\+

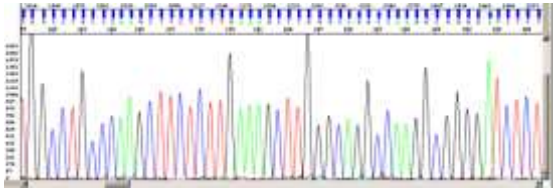
Second hit?



APOL1 kidney disease

Beckerman P, et al. *Nat Med*. 2017;23(4):429–8

Why do only some people with the APOL1 high-risk genotype get disease?

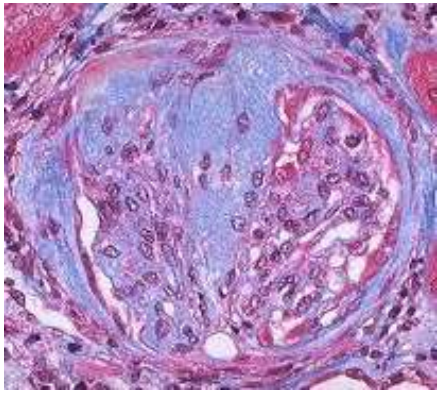


APOL1 high-risk genotype

\+

Second hit?

HIV
Covid-19
lupus
interferon

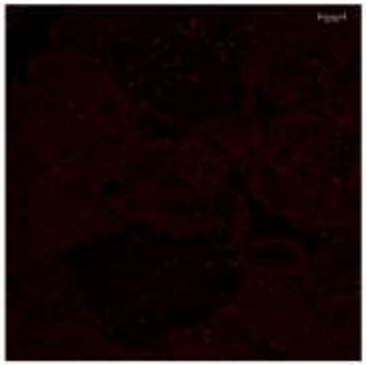


APOL1 kidney disease

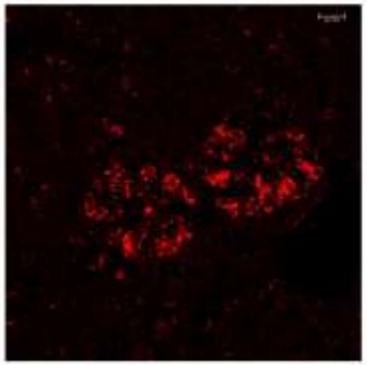
Both the high-risk genotype and elevated APOL1 expression are likely needed to cause kidney disease

Beckerman P, et al. *Nat Med*. 2017;23(4):429–8

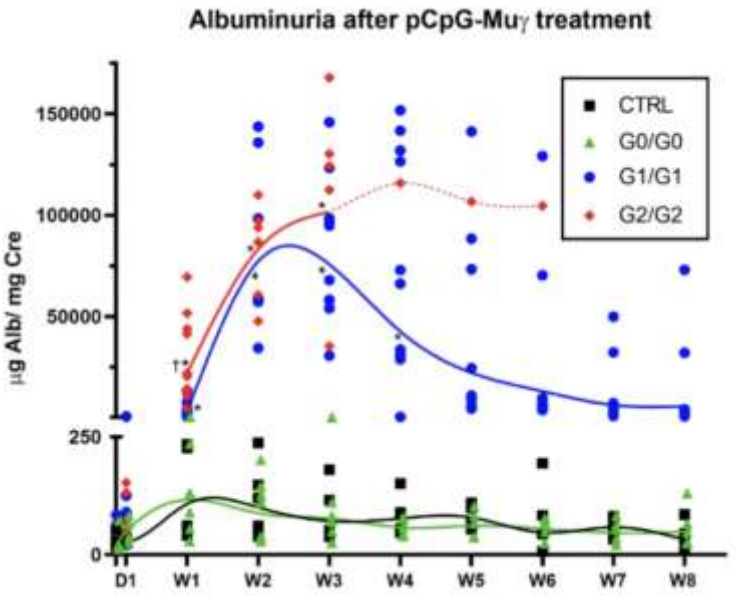
Interferon turns on APOL1 expression and causes kidney injury

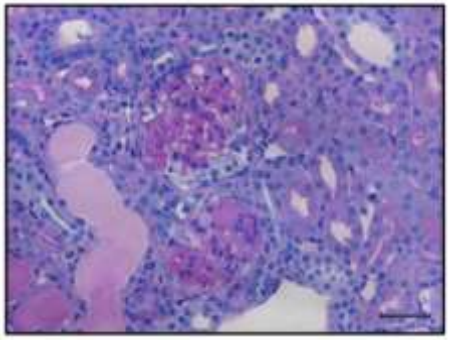


Interferon

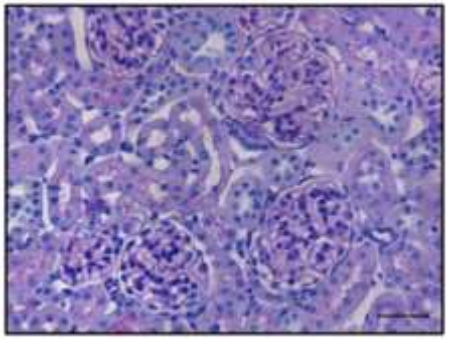


APOL1





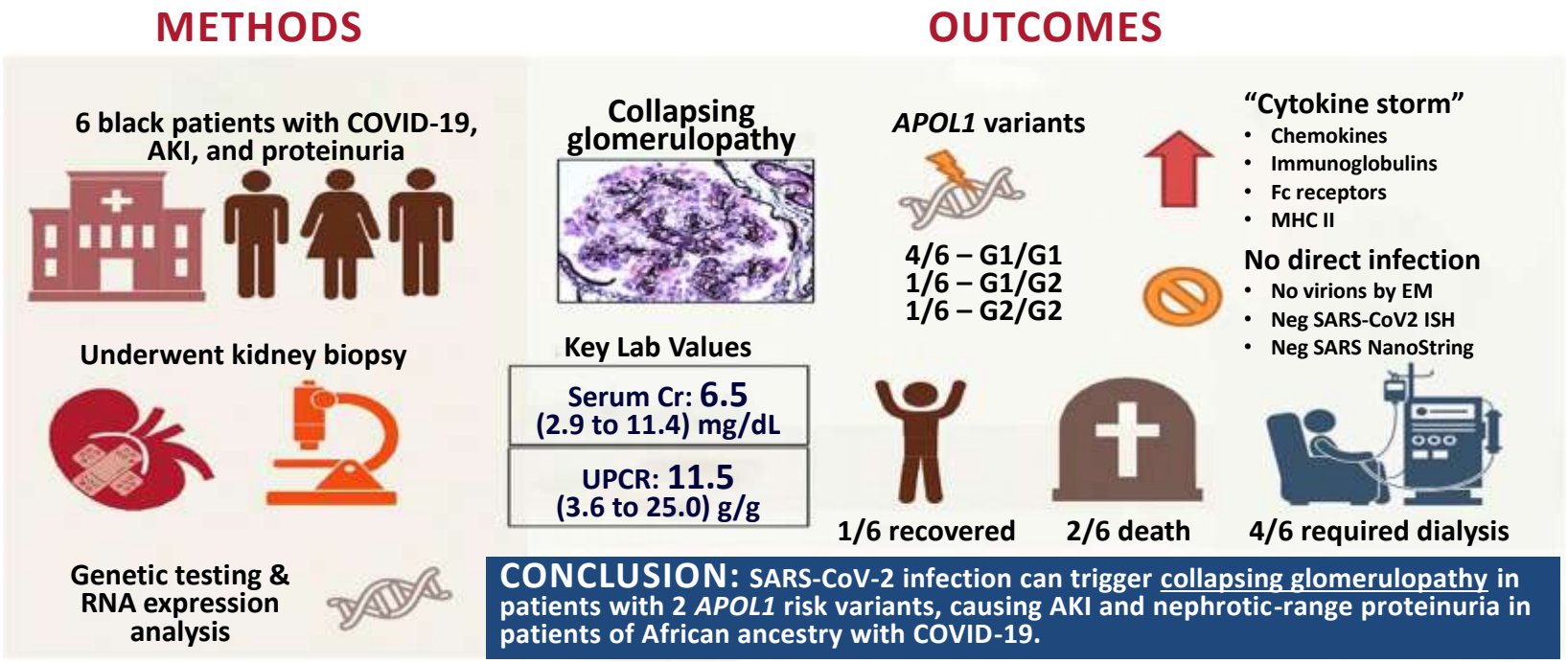
G2/G2 mouse



G0/G0 mouse

McCarthy GM, et al. *Dis Model Mech*. 2021;14(8):dmm048952

AKI and Collapsing Glomerulopathy Associated with COVID-19 and *APOL1* HIGH-RISK Genotype



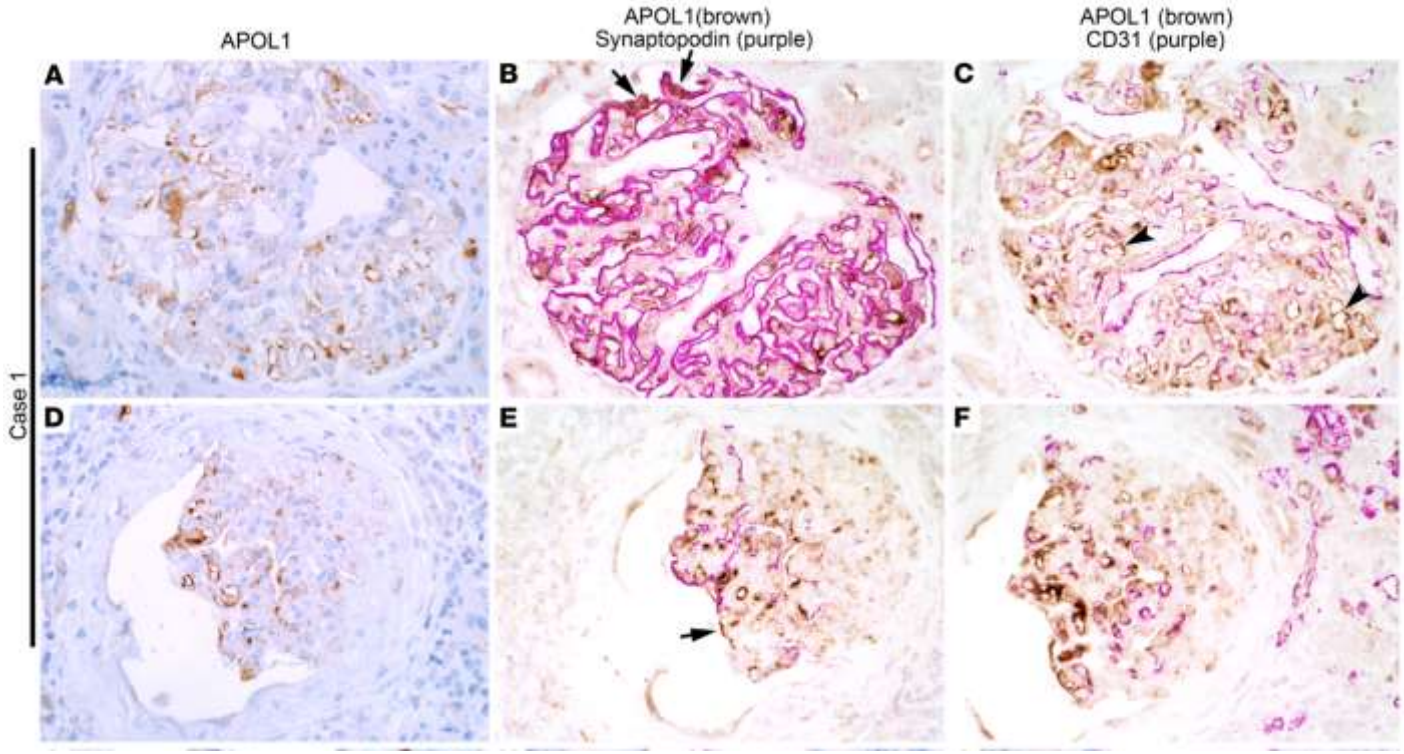
Wu H, et al. *J Am Soc Nephrol*. 2020;31:1688-1695.

JCI insight

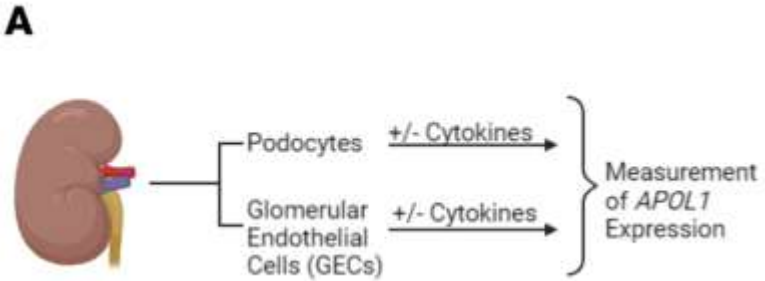
JAK inhibitor blocks COVID-19 cytokine–induced JAK/STAT/APOL1 signaling in glomerular cells and podocytopathy in human kidney organoids

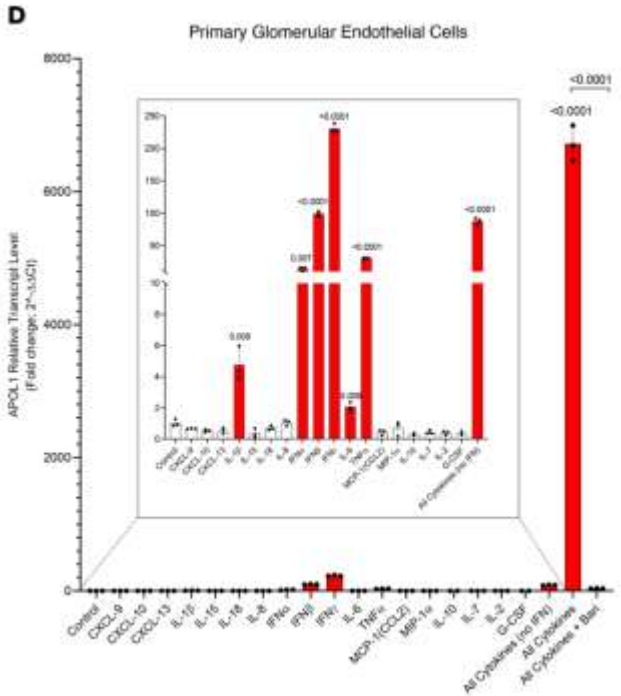
Sarah E. Nystrom, … , David B. Thomas, Opeyemi A. Olabisi

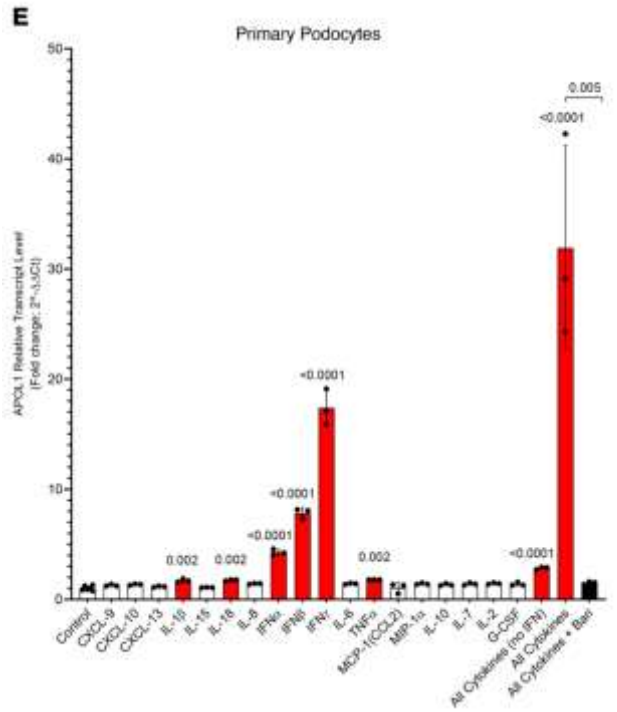
JCI Insight. 2022;7(11):e157432. https://doi.org/10.1172/jci.insight.157432.



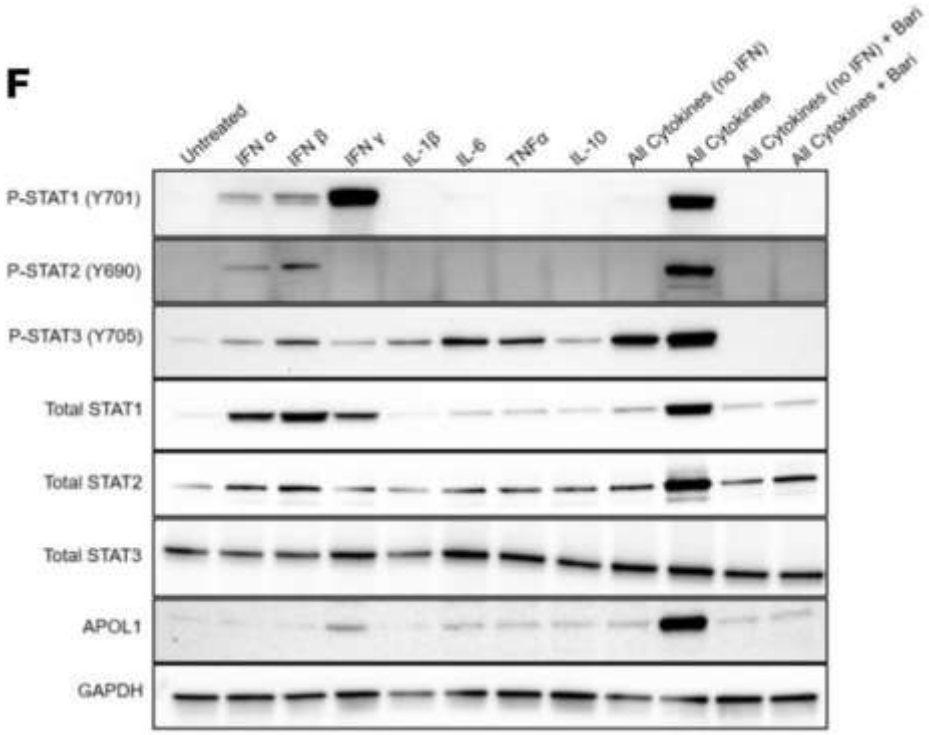
Cytokines storm induces Apol1 expression in GEC and Podocytes



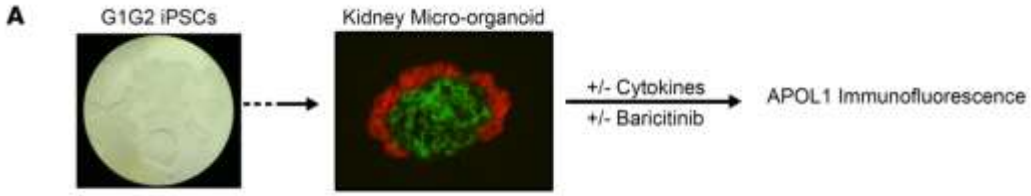


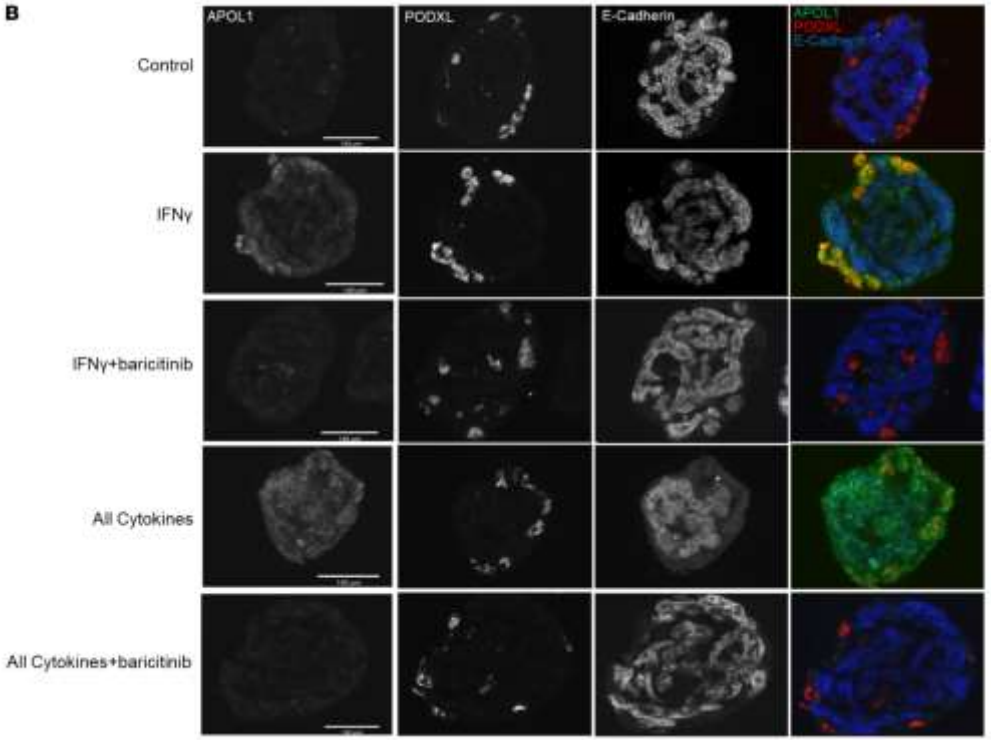


....And activates the JAK-STAT pathway

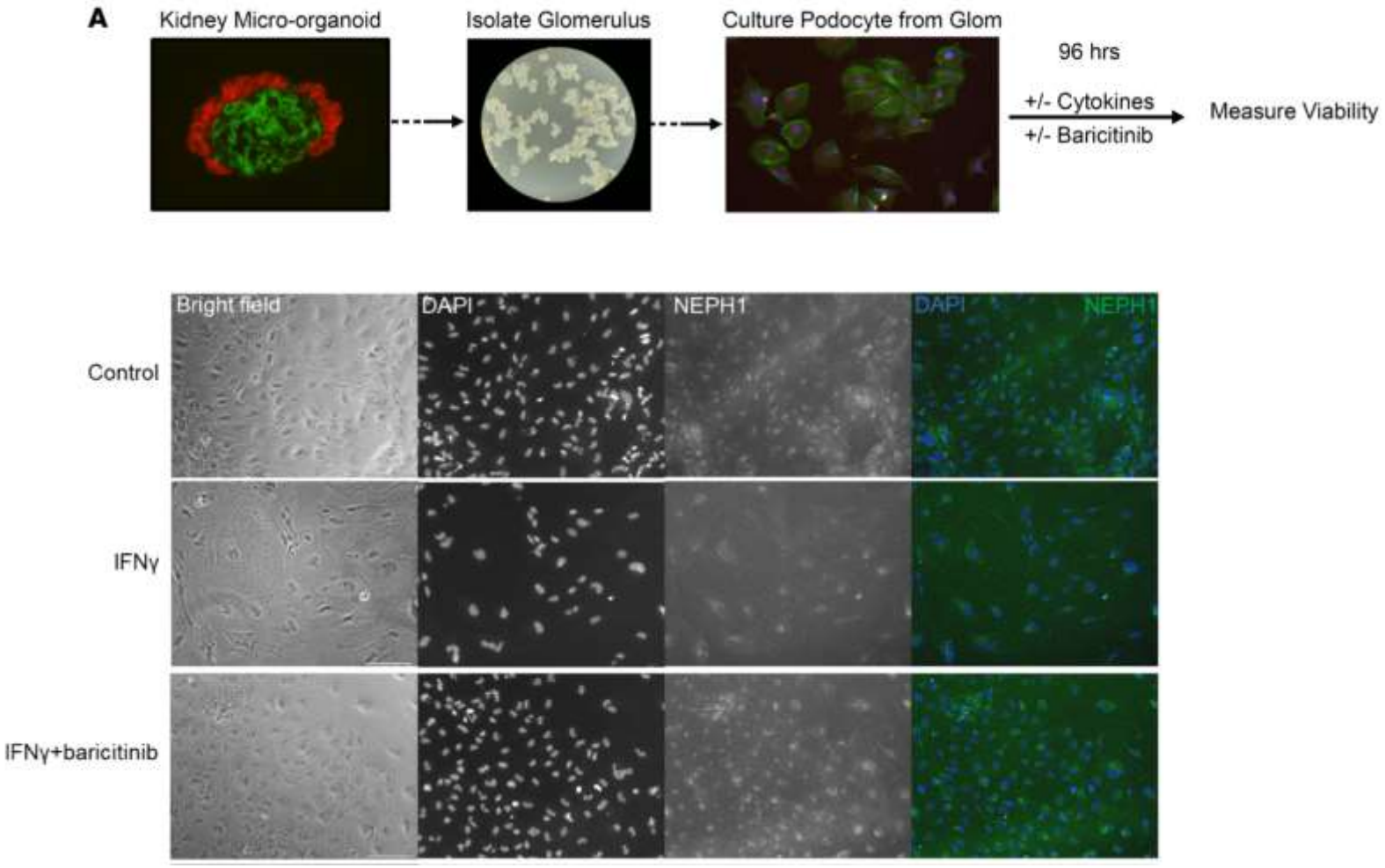


COVID-19–induced cytokines are sufficient to drive APOL1 expression in human iPSC kidney micro-organoids, which is blocked by inhibition of the JAK/STAT/APOL1 axis (Baricitinib)

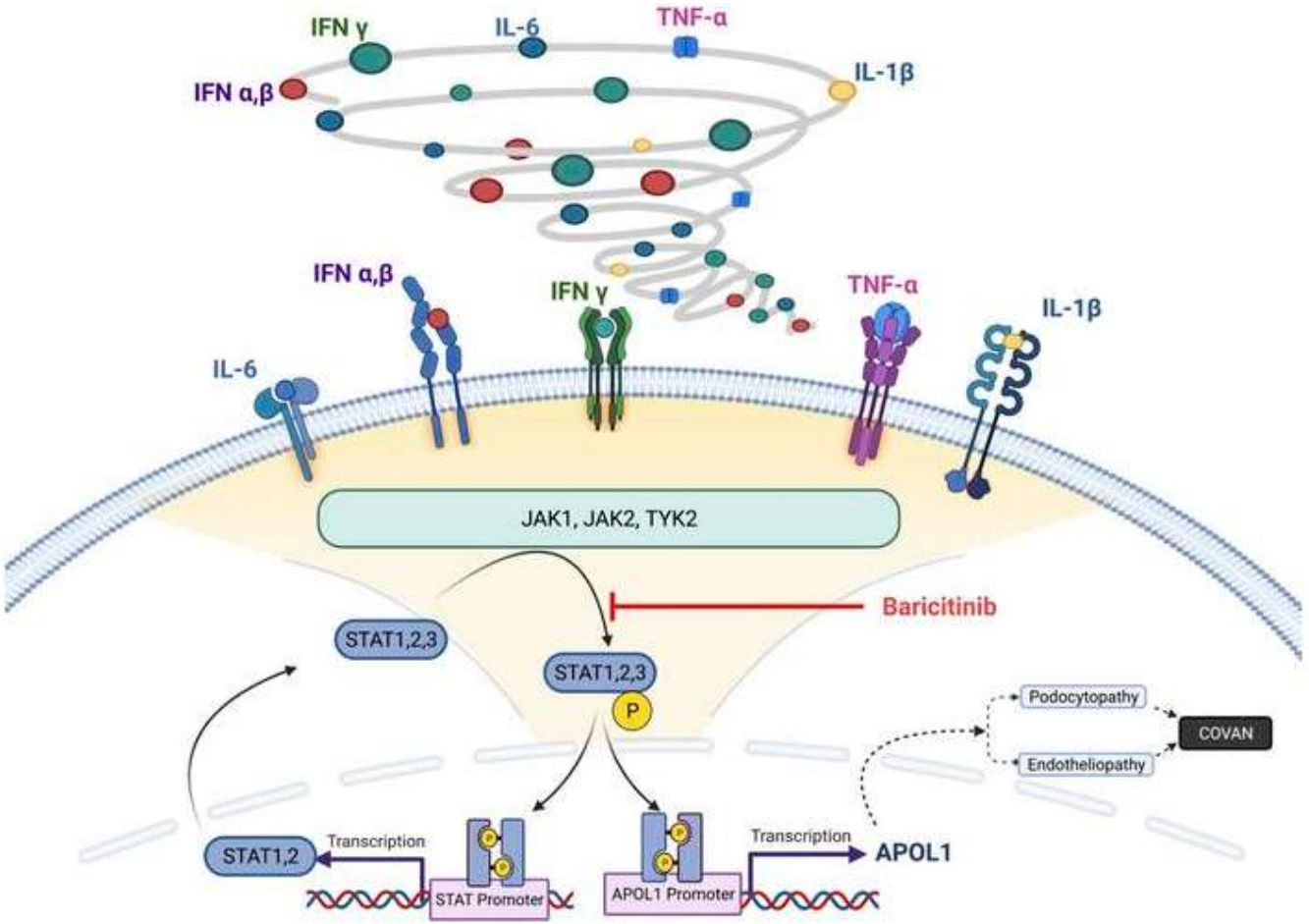




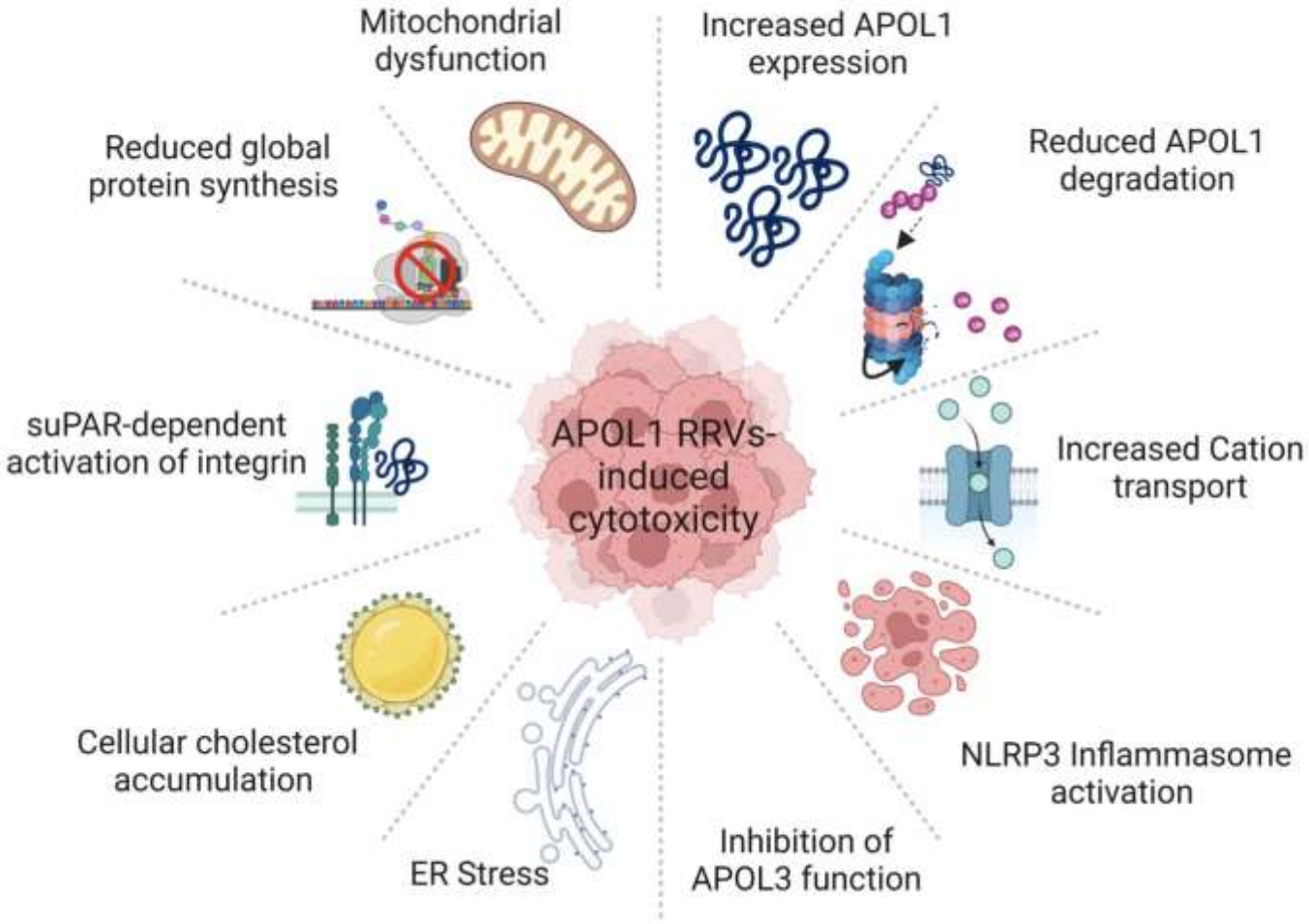
Cytokine-induced *APOL1* expression correlates with significantly decreased viability and cellular metabolism in organoid-derived podocytes (G1G2)



Conclusion:
JAK/STAT pathway inhibition as a new target for Apol1 assocaited kidney disease



Current theories of the mechanisms of APOL1-induced cytotoxicity

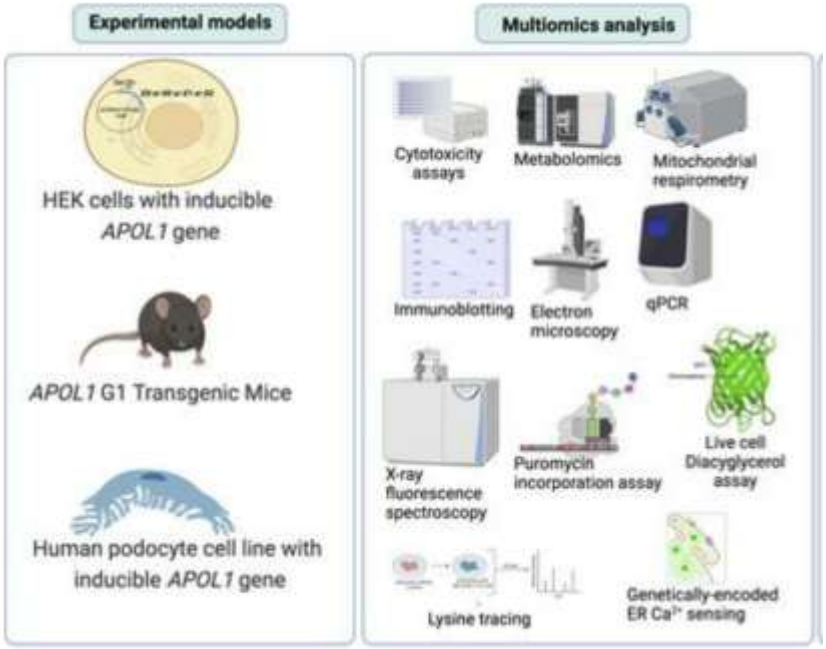


JCI The Journal of Clinical Investigation

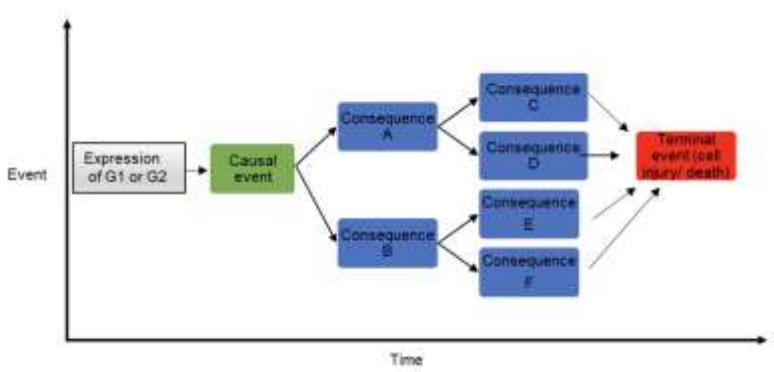
APOL1-mediated monovalent cation transport contributes to APOL1-mediated podocytopathy in kidney disease

Somenath Datta, … , Christopher B. Newgard, Opeyemi A. Olabisi

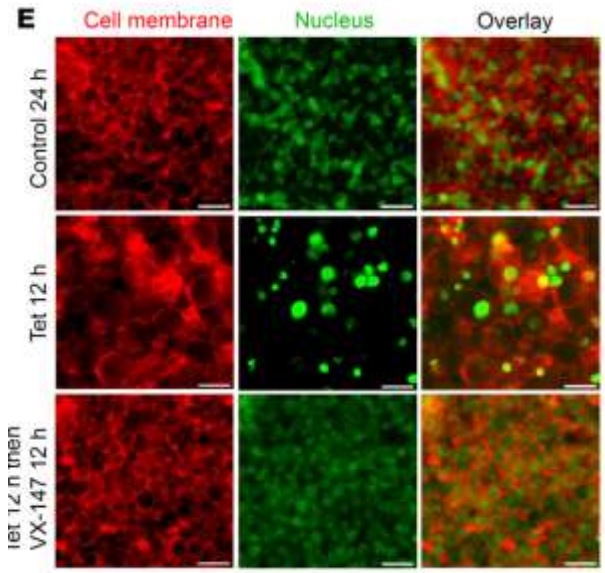
J Clin Invest. 2024;134(5):e172262. https://doi.org/10.1172/JCI172262.



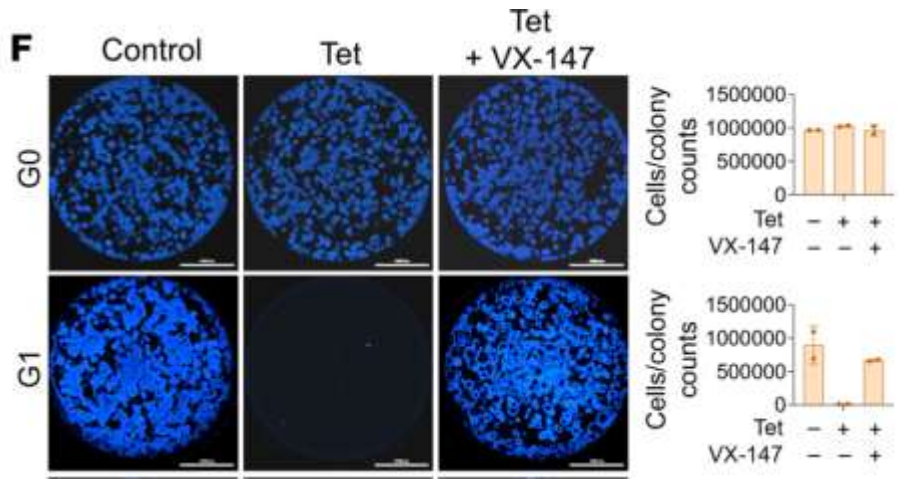
B.



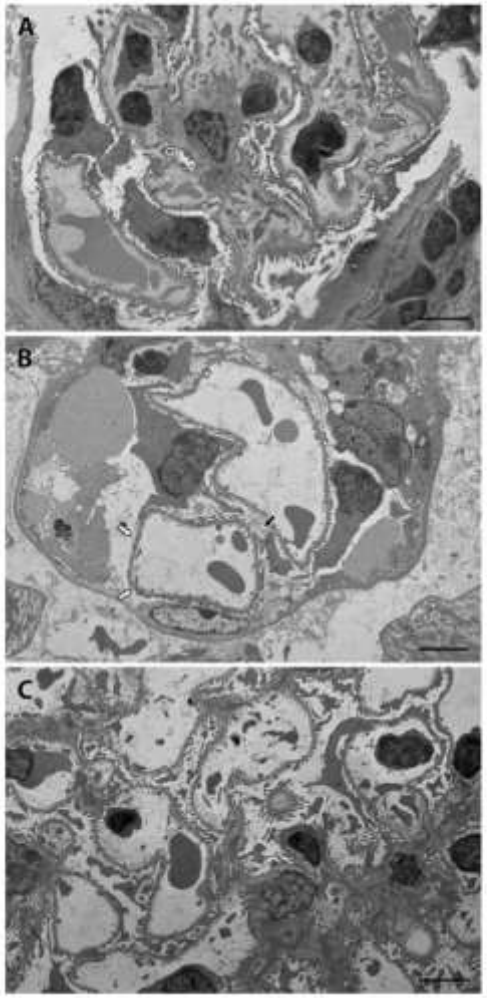
Cell swelling is inhibited by VX-147



G1 induced Cell death Is rescued by VX-147



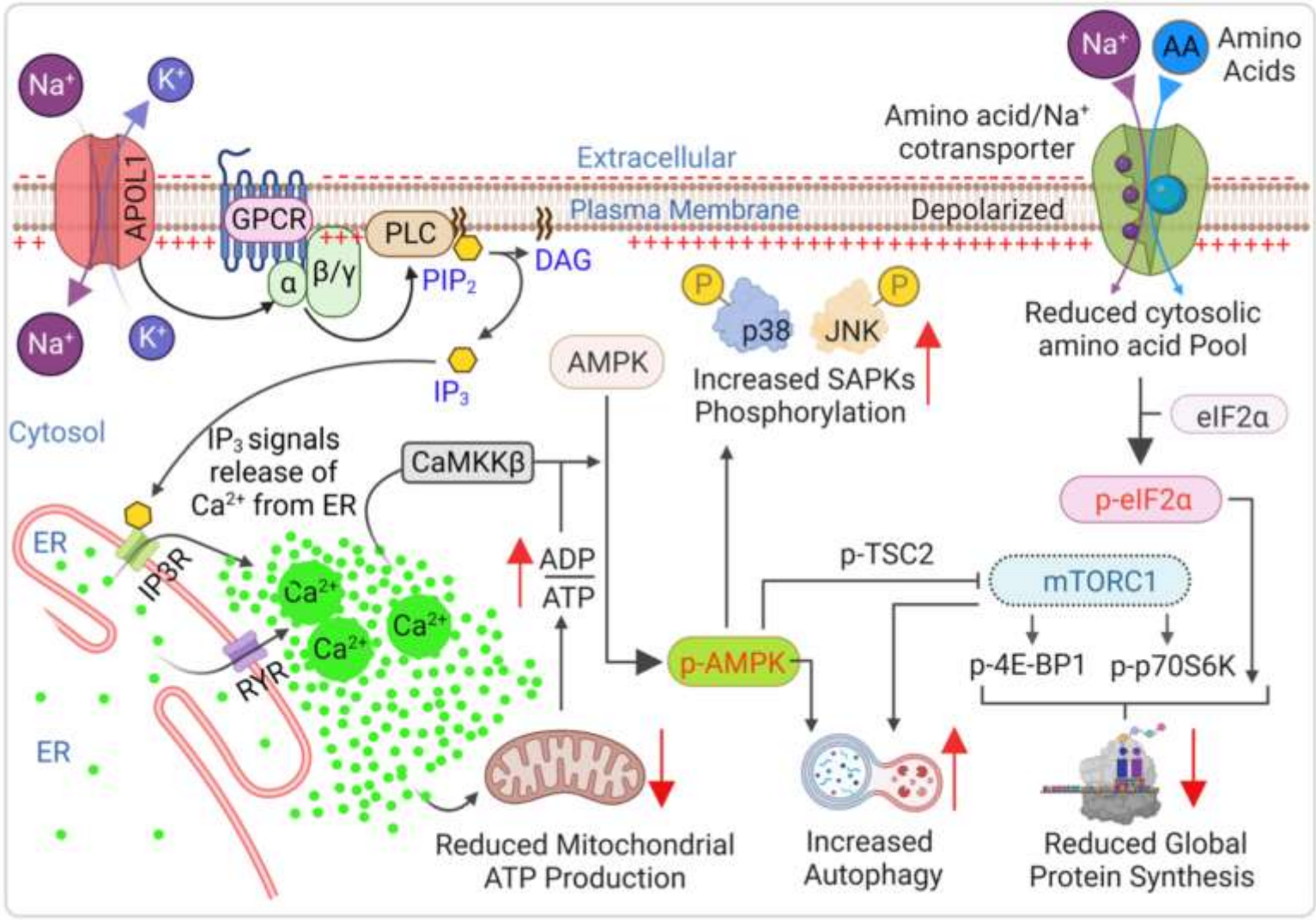
Electron micrograph of APOL1 G1 transgenic mice.

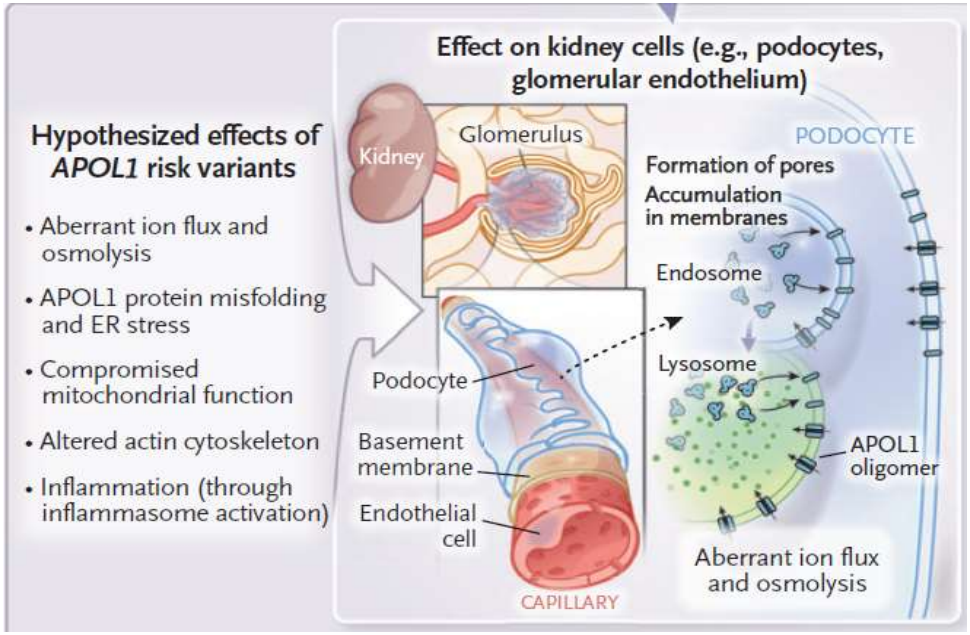


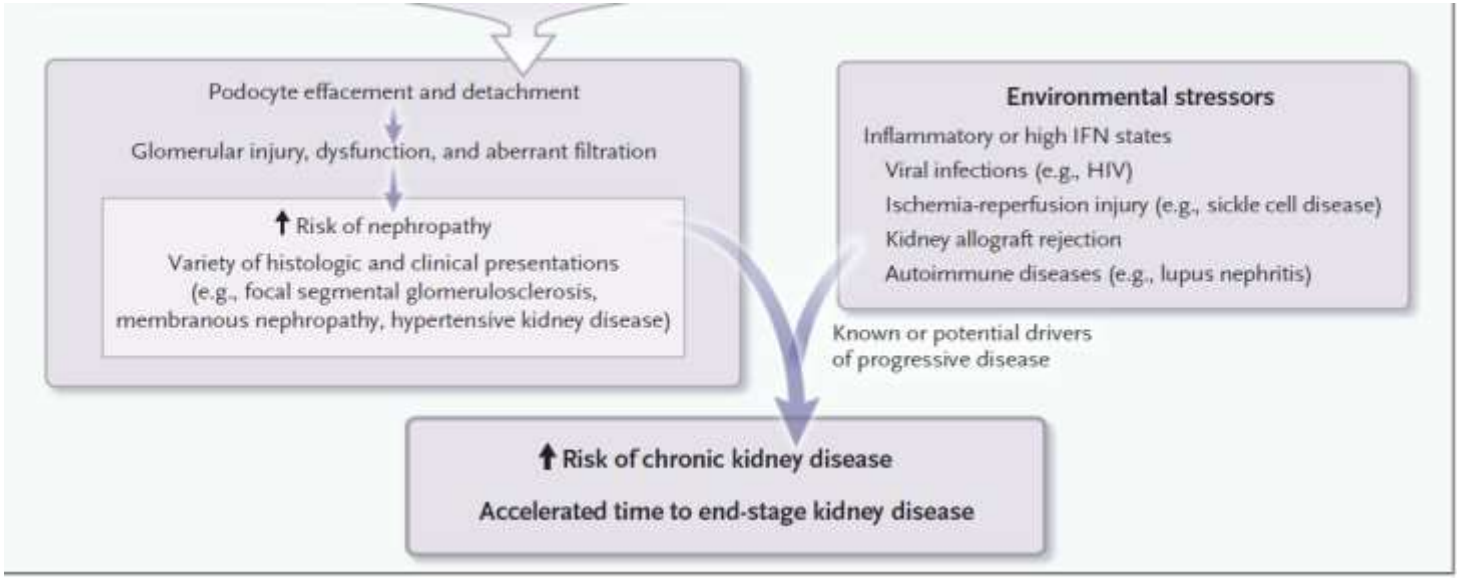
FNγ-treated mice (B) have focal podocyte foot process effacement (white arrow), microvillous transformation (black arrow), and cytoplasmic shedding (white arrowhead).

Treatment with VX- 147 (C) rescued the cellular phenotypes.

Proposed mechanism of APOL1 RRVs-induced cytotoxicity







Williams WW, IngelfingerJ, NEJM, 388;11 nejm.org March 16, 2023

Therapeutic considerations

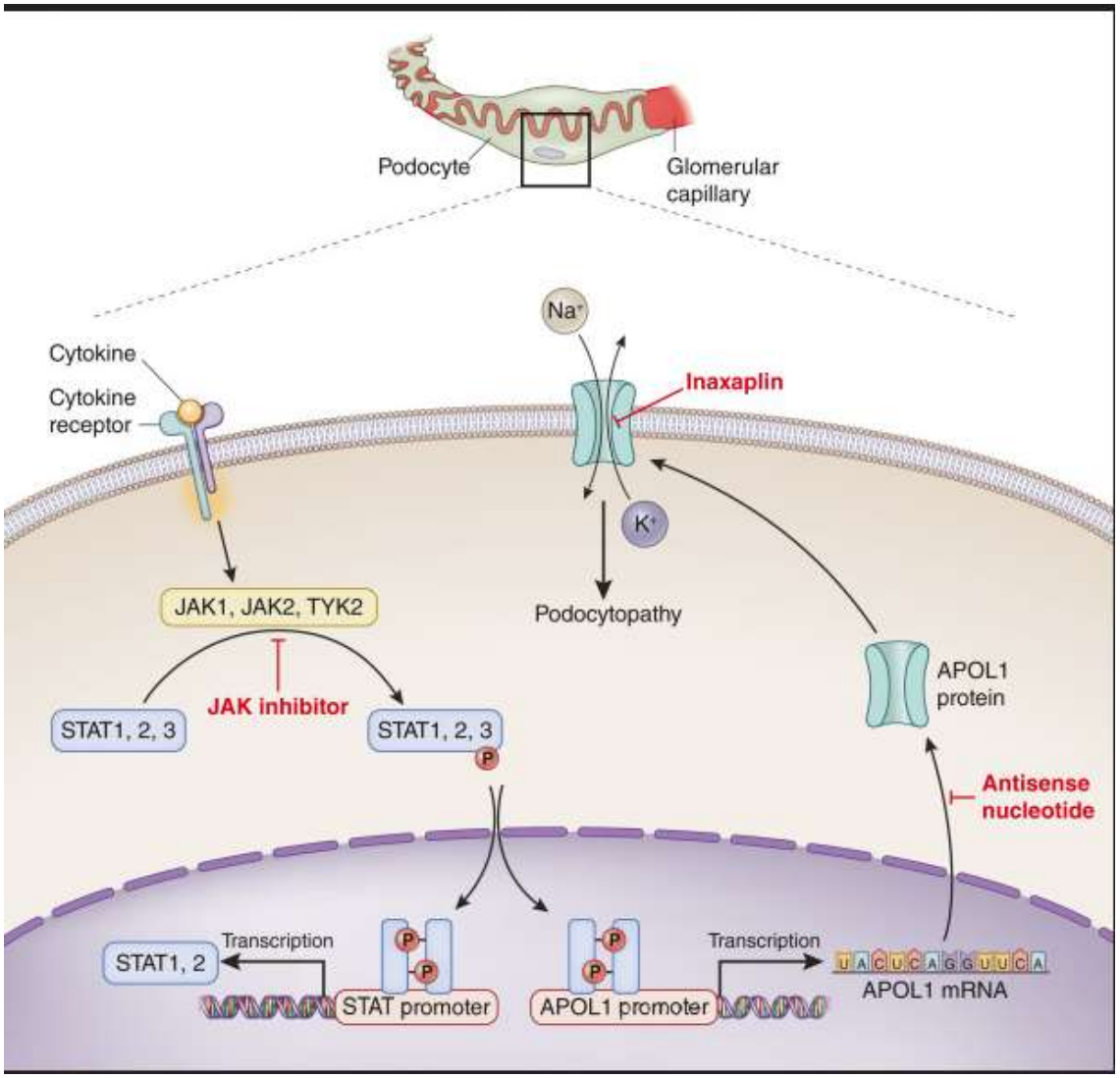
Challenges:

- Exact mechanism unclear
- Normal function unknown
- Cell type not certain

Advantages:

- Gain-of-function
- Not essential for kidney function
- Genetically-validated
- Modulate activity at many levels

Potential Therapies for Apol1 associated Kidney Diseases



Olabisi O, KI, 2023

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 16, 2023 VOL. 388 NO. 11

Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants

O. Egbuna, B. Zimmerman, G. Manos, A. Fortier, M.C. Chirieac, L.A. Dakin, D.J. Friedman, K. Bramham, K. Campbell, B. Knebelmann, L. Barisoni, R.J. Falk, D.S. Gipson, M.S. Lipkowitz, A. Ojo, M.E. Bunnage, M.R. Pollak, D. Altshuler, and G.M. Chertow, for the VX19-147-101 Study Group*

SCIENCE BEHIND THE STUDY

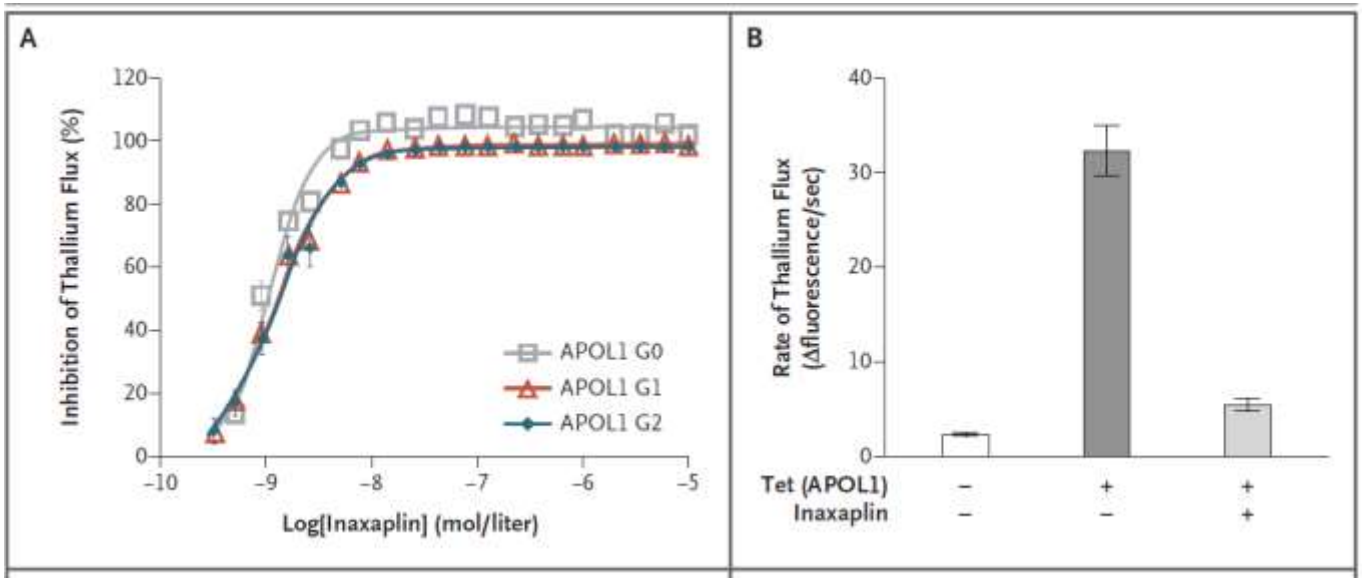
Inhibiting APOL1 to Treat Kidney Disease

Winfred W. Williams, M.D., and Julie R. Ingelfinger, M.D.

A Step Forward for Precision Equity in Kidney Disease

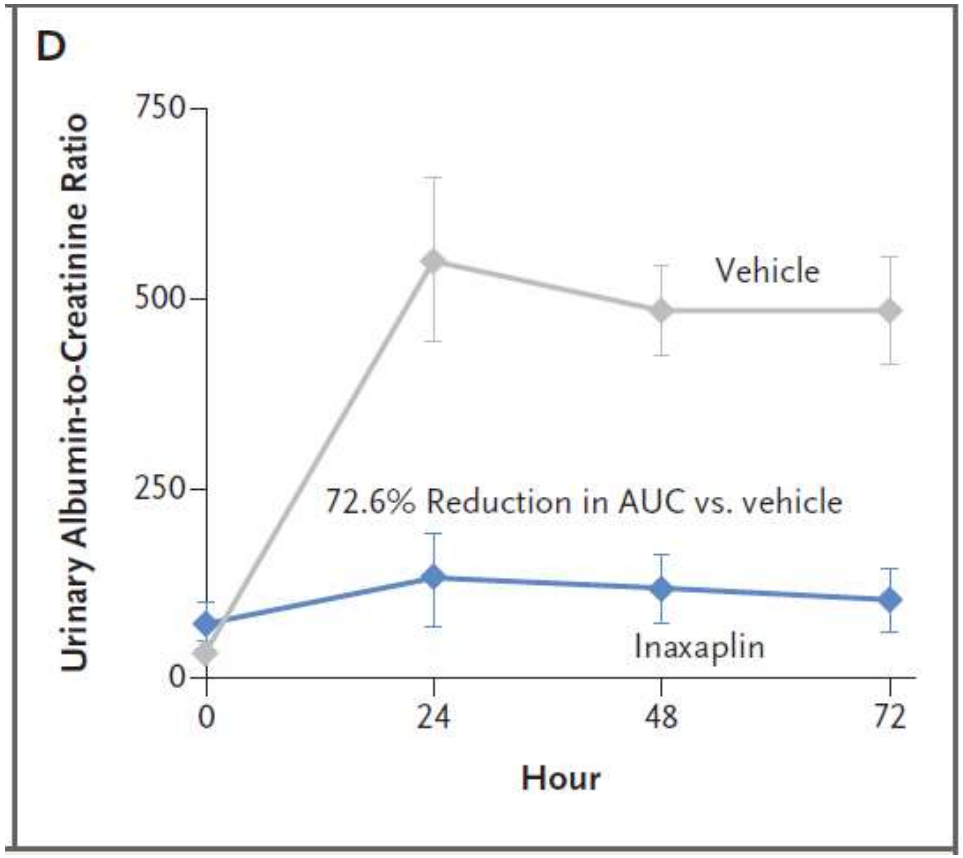
Neil R. Powe, M.D.

In vitro, VX-147 inhibits ApoL1 mediated Thallium flux



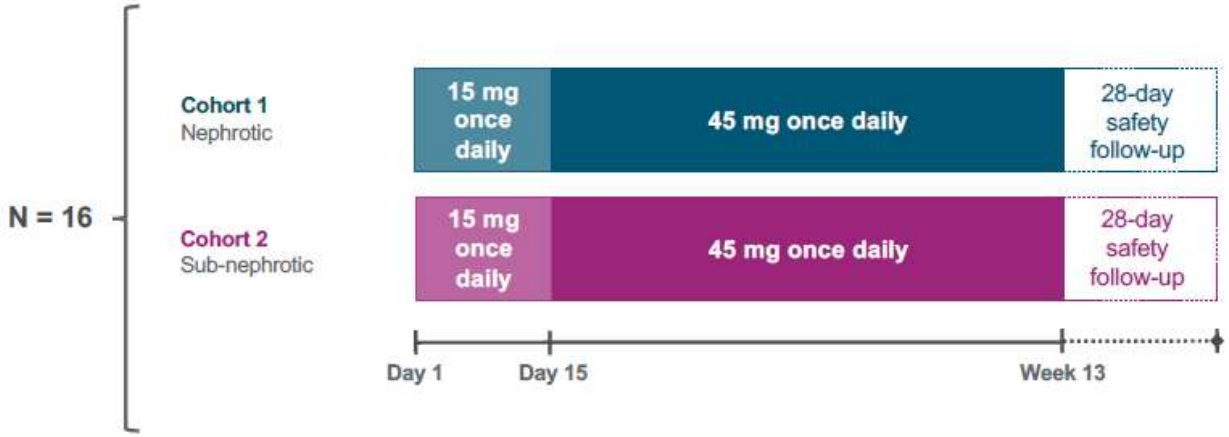
Egbuna O et al, n engl j med 388;11 nejm.org March 16, 2023

VX-147 decreases INF induced Proteinuria in Apol1 G2 homozygotes mice



Egbuna O et al, n engl j med 388;11 nejm.org March 16, 2023

VX-147 PHASE 2 PROOF OF CONCEPT STUDY OVERVIEW



- **Primary Objective:** Evaluate ability of VX-147 to reduce proteinuria in patients with APOL1-mediated FSGS
- **Primary endpoint:** % change from baseline in UPCR (proteinuria) at week 13
- **Secondary endpoint:** Safety and tolerability; plasma pharmacokinetics

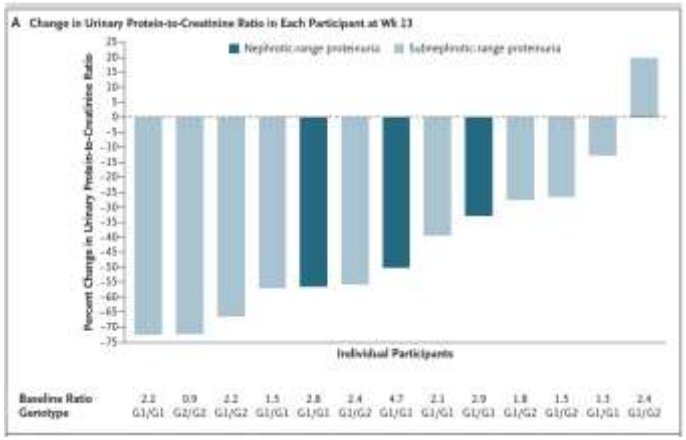
Inclusion criteria

- Adults ≥18 years to ≤65 years with 2 APOL1 genetic variants and biopsy-confirmed FSGS
- eGFR ≥27 ml/min/1.73 m^2
- Nephrotic range proteinuria: baseline UPCR ≥2.7 to <10 g/g
- Sub-nephrotic range proteinuria: baseline UPCR ≥ 0.7 to <2.7 g/g
- Allowed to be on a stable regimen of standard of care medication

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Total (N = 16)	Participants with Nephrotic-Range Proteinuria (N=3)	Participants with Subnephrotic-Range Proteinuria (N=13)
Age — yr	38.8±14.5	45.0±10.5	37.3±15.2
Sex — no. (%)			
Male	7 (44)	1 (33)	6 (46)
Female	9 (56)	2 (67)	7 (54)
APOL1 genotype — no. (%)			
G1/G1	9 (56)	3 (100)	6 (46)
G2/G2	1 (6)	0	1 (8)
G1/G2	6 (38)	0	6 (46)
Body-mass index	29.6±6.4	32.7±6.4	28.9±6.4
Urinary protein-to-creatinine ratio†	2.08±0.90	3.47±1.07	1.77±0.49
Estimated GFR — ml/min/1.73 m^2	51.2±14.0	51.4±22.2	51.2±12.8
Standard-care medication			
ACE inhibitor			
≥28 days before day 1 — no. (%)	8 (50)	1 (33)	7 (54)
On day 1 — no./total no. (%)	8/8 (100)	1/1 (100)	7/7 (100)
Angiotensin-receptor blocker			
≥28 days before day 1 — no. (%)	7 (44)	3 (100)	4 (31)
On day 1 — no./ total no. (%)	6/7 (86)	2/3 (67)‡	4/4 (100)
Immunosuppressants§			
≥28 days before day 1 — no. (%)	4 (25)	1 (33)	3 (23)
On day 1 — no./ total no. (%)	4/4 (100)	1/1 (100)	3/3 (100)

Figure 2. Efficacy Outcomes: Data for 13 evaluable participants



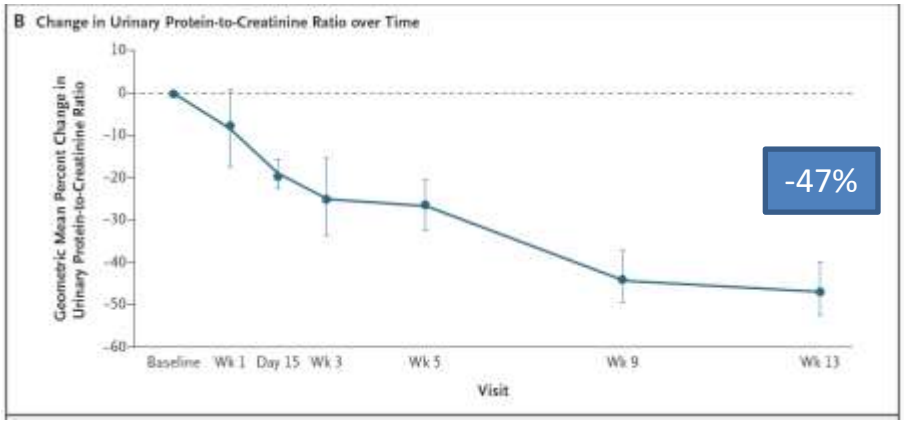
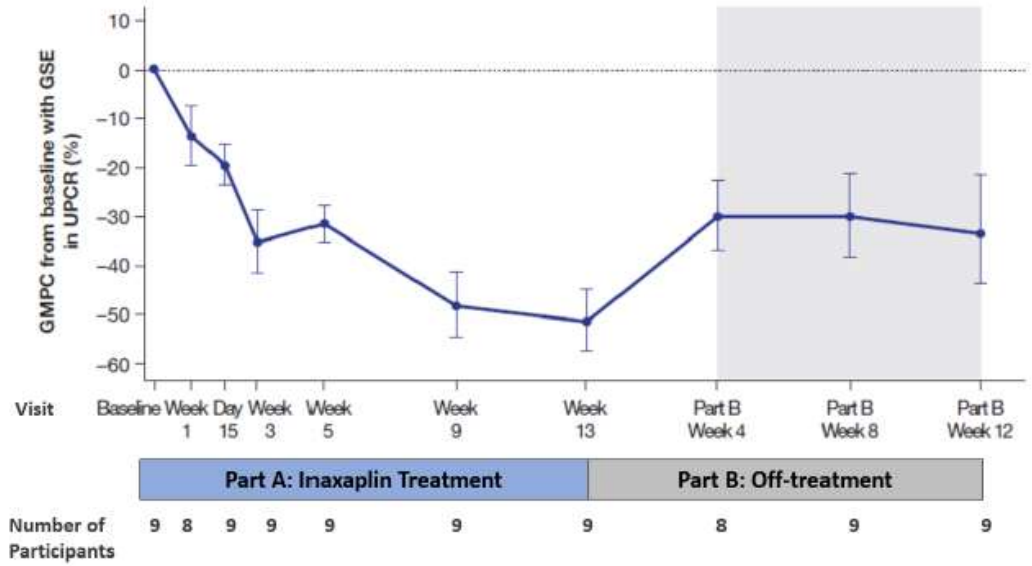


Table 2. Mean Percent Change from the Baseline Urinary Protein-to-Creatinine Ratio at Week 13.*

Variable	Total (N = 13)	Participants with Nephrotic-Range Proteinuria (N = 3)	Participants with Subnephrotic-Range Proteinuria (N = 10)
Mean urinary protein-to-creatinine ratio			
At baseline	2.21±0.95	3.47±1.07	1.84±0.52
At wk 13	1.27±0.73	1.83±0.58	1.10±0.71
Geometric percent change from baseline at wk 13 (95% CI)	−47.6 (−60.0 to −31.3)	−47.7 (−70.1 to −8.5)	−47.5 (−63.4 to −24.6)

* Plus–minus values are means ±SD. Baseline and week 13 assessments of the urinary protein-to-creatinine ratio for each of the participants were calculated as the mean of three first-morning void measurements obtained within a 7-day window. The efficacy analysis set included all the participants who completed inaxaplin treatment and had at least 80% adherence to treatment. CI denotes confidence interval.

Egbuna O et al, n engl j med 388;11 nejm.org March 16, 2023



Part B : 9 participants

- Mean UPCR increased from −47.6% to −30.1% at week 4
- and remained stable untill wk 12

Very good safety profile in phase 2

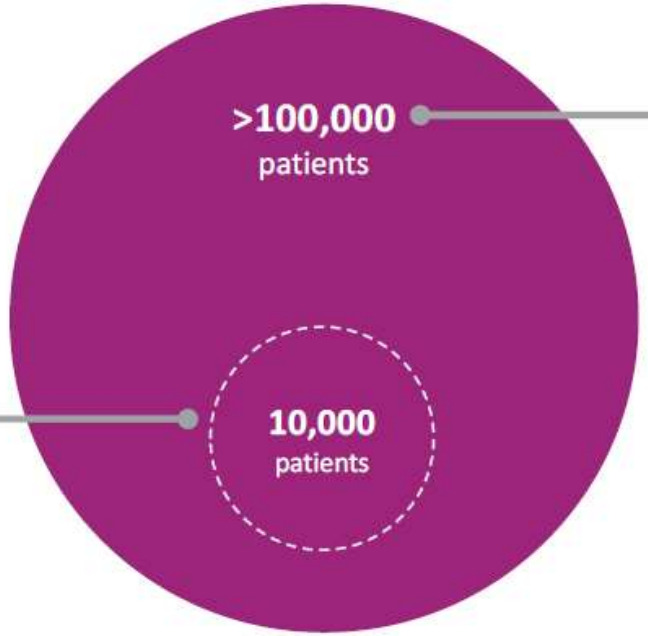
Table 3. Adverse Events.*

Event	Total (N = 16)
Any adverse event†	15 (94)
Adverse events according to severity	
Mild	7 (44)
Moderate	8 (50)
Severe	0
Life-threatening	0
Serious adverse event‡	1 (6)
Adverse event leading to treatment discontinuation	0
Adverse event occurring in ≥2 participants	
Headache	4 (25)
Back pain	3 (19)
Nausea	3 (19)
Decrease in blood bicarbonate level	2 (12)
Diarrhea	2 (12)
Dizziness	2 (12)
Dyspepsia	2 (12)
Fatigue	2 (12)

Egbuna O et al, n engl j med 388;11 nejm.org March 16, 2023

APOL1-MEDIATED KIDNEY DISEASE IS A GENETICALLY DEFINED CONDITION

APOL1-mediated kidney disease includes different clinical/histological presentations with the same genetic cause



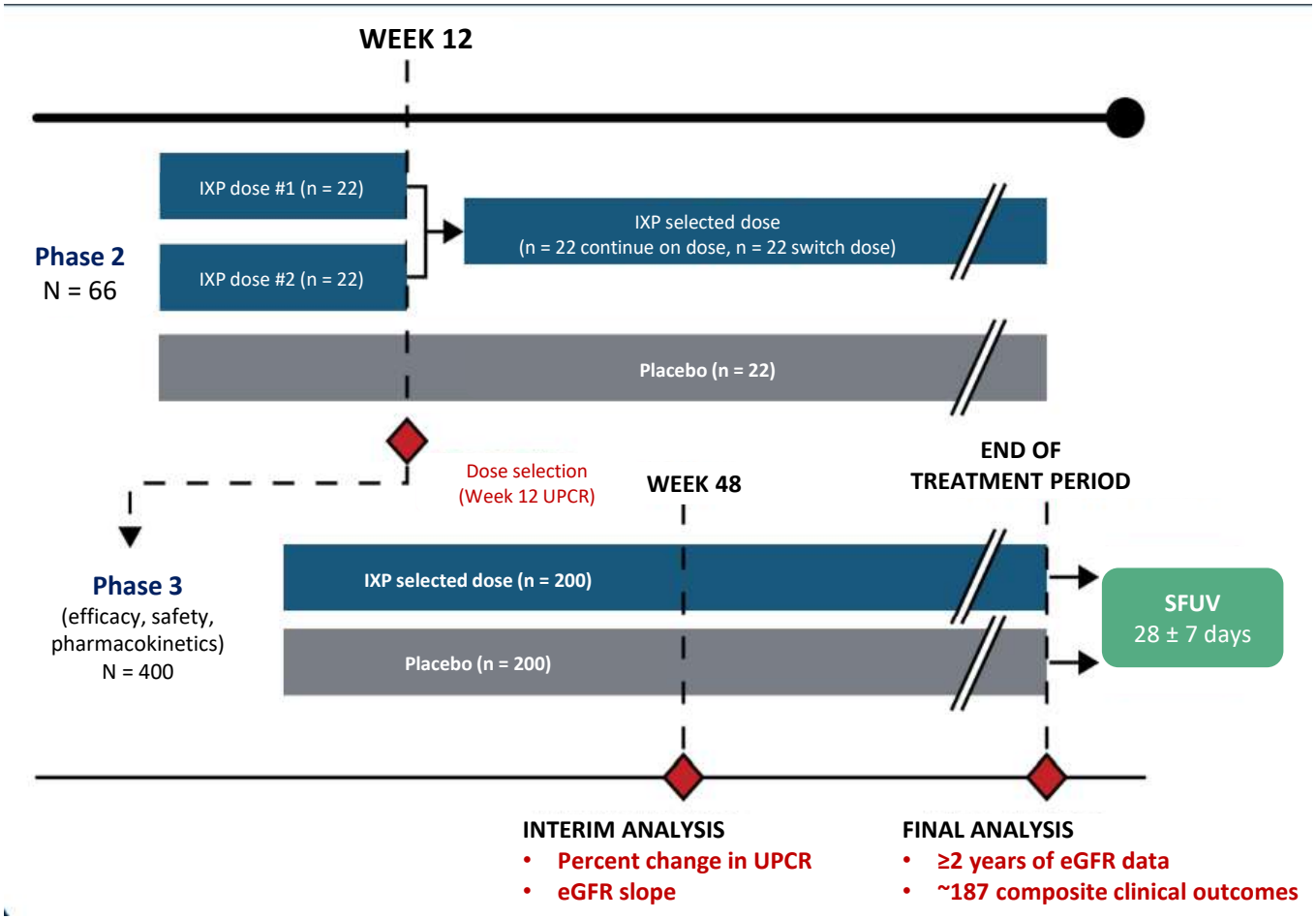
APOL1-MEDIATED KIDNEY DISEASE

- **Broader** population
  - Includes APOL1-mediated FSGS
- Moderate to heavy proteinuria
- Clinically diagnosed
- Two APOL1 mutations

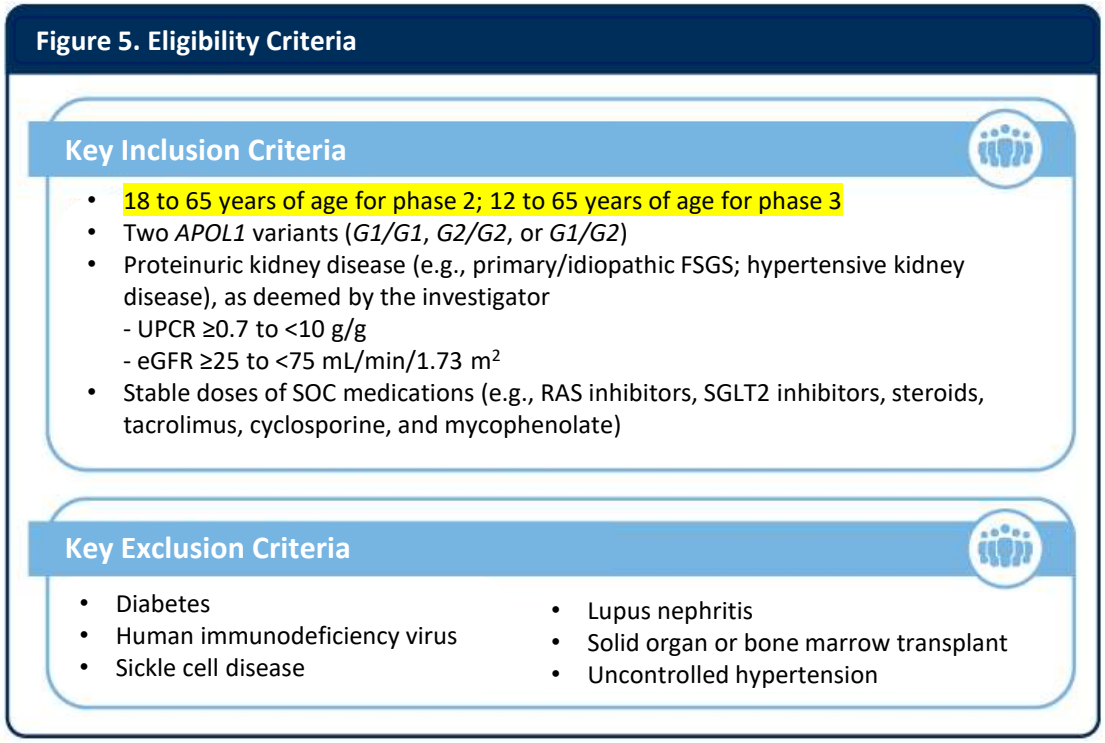
APOL1-MEDIATED FSGS

- **Narrower** population
- Heavy proteinuria
- Biopsy-diagnosed
- Two APOL1 mutations

Design of the Phase 2/3 AMPLITUDE Adaptive Clinical Trial



Clinical Trial Design



APOL1: *Apolipoprotein L1*; eGFR: estimated glomerular filtration rate; FSGS: focal segmental glomerulosclerosis; RAS: renin-angiotensin system; SOC: standard-of-care; SGLT2: sodium-glucose cotransporter 2; UPCR: urine protein to creatinine ratio

VX21-147-301 study

ENDPOINTS

Primary

- Percent change in UPCR from baseline at Week 48 (assessed at the IA)
- eGFR slope (with ≥48 weeks of eGFR data assessed at the IA and at least 2 years of eGFR data assessed at the final analysis)

Secondary

- Time to composite clinical outcome of:
  - Sustained* decline of ≥30% in eGFR from baseline
  - Onset of ESKD:
    - Maintenance dialysis for ≥28 days
    - Kidney transplantation
    - Sustained* eGFR of <15 ml/min/1.73m^2
  - Death
- Safety and tolerability based on AEs, clinical laboratory values (i.e., hematology, serum chemistry, coagulation studies, urinalysis), standard 12-lead ECGs, and vital signs
- Plasma PK parameters of VX-147

* "Sustained" is defined as confirmation by a second measurement after ≥28 days

UPCR: Urinary Protein-to-Creatinine Ratio; eGFR: estimated glomerular filtration rate; AE: Adverse Event; ECG: Electrocardiogram

VERTEX

Vertex Advances Inaxaplin (VX-147) into Phase 3 Portion of Adaptive Phase 2/3 Clinical Trial for the Treatment of APOL1-Mediated Kidney Disease

April 1, 2024

– 45 mg once daily oral dose selected for Phase 3 – (IDMC)

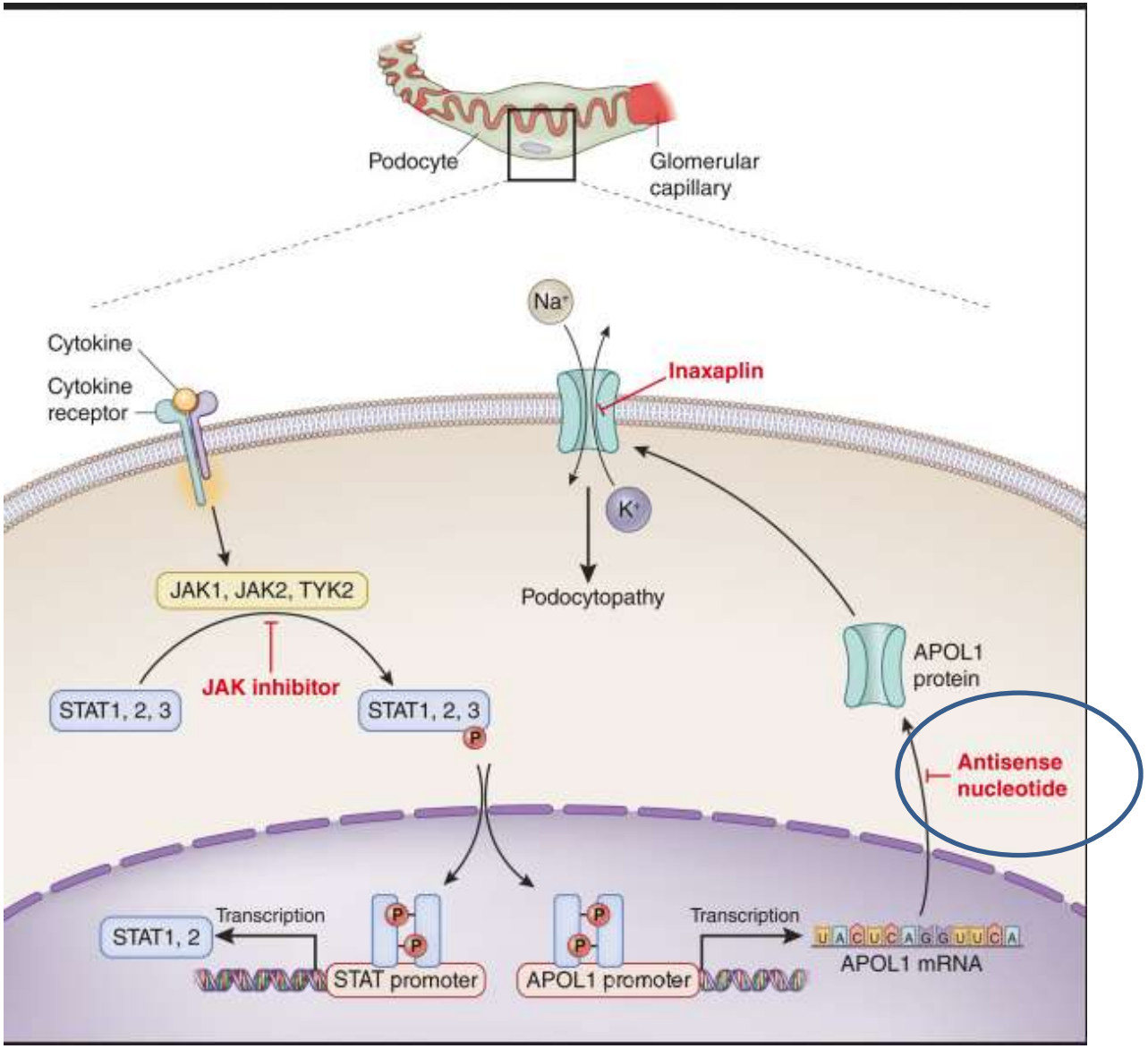
– Results support trial expansion to lower age group and study will now include adolescents ages 10-17 years –

– If positive, pre-planned interim analysis at Week 48 may serve as the basis for accelerated approval in the U.S. –

& The FDA has granted inaxaplin Rare Pediatric Disease Designation (RPD) and Breakthrough Therapy Designation (BTD) for APOL1-mediated focal segmental glomerulosclerosis (FSGS).

& The EMA has also granted inaxaplin Priority Medicines (PRIME) and Orphan Drug designations for AMKD

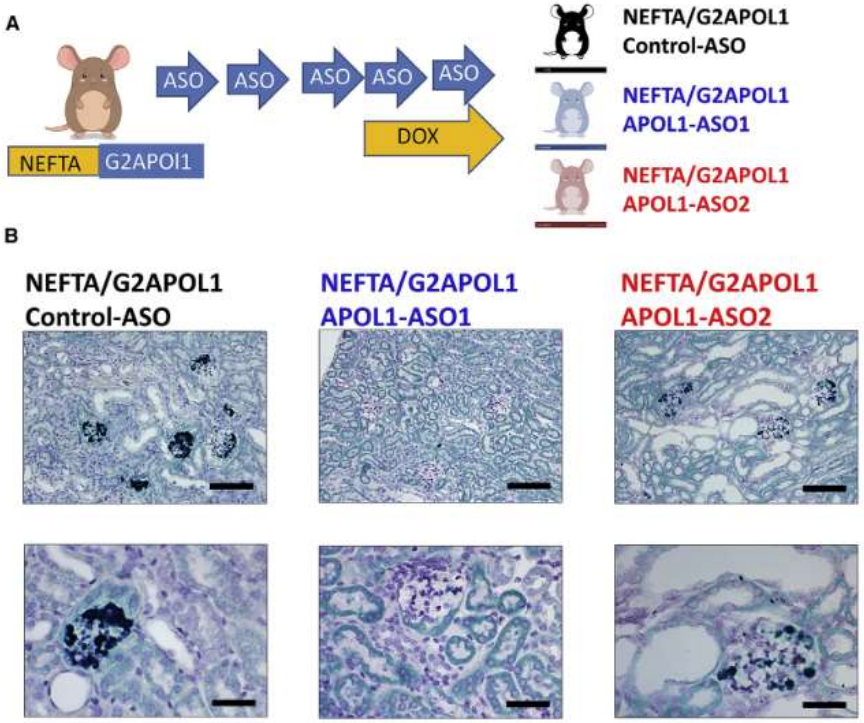
Potential Therapies for Apol1 associated KD

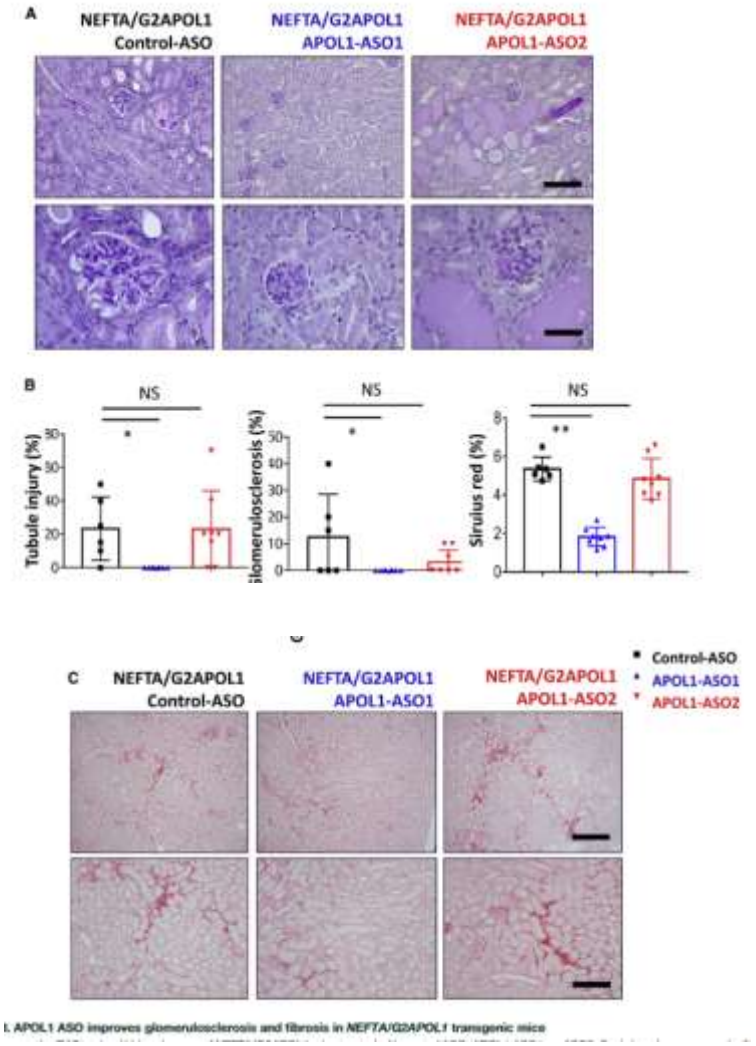


Molecular Therapy
Original Article

Antisense oligonucleotides ameliorate kidney dysfunction in podocyte-specific APOL1 risk variant mice

Ya-Wen Yang,[1,2,6] Bibek Poudel,[1,6] Julia Frederick,[1] Poonam Dhillon,[1] Rojesh Shrestha,[1] Ziyuan Ma,[1] Junnan Wu,[1] Koji Okamoto,[3] Jeffrey B. Kopp,[3] Sheri L. Booten,[4] Danielle Gattis,[5] Andrew T. Watt,[5] Matthew Palmer,[5] Mariam Aghajan,[5] and Katalin Susztak[1]





l. APOL1 ASO improves glomerulosclerosis and fibrosis in *NEFTA/G2APOL1* transgenic mice

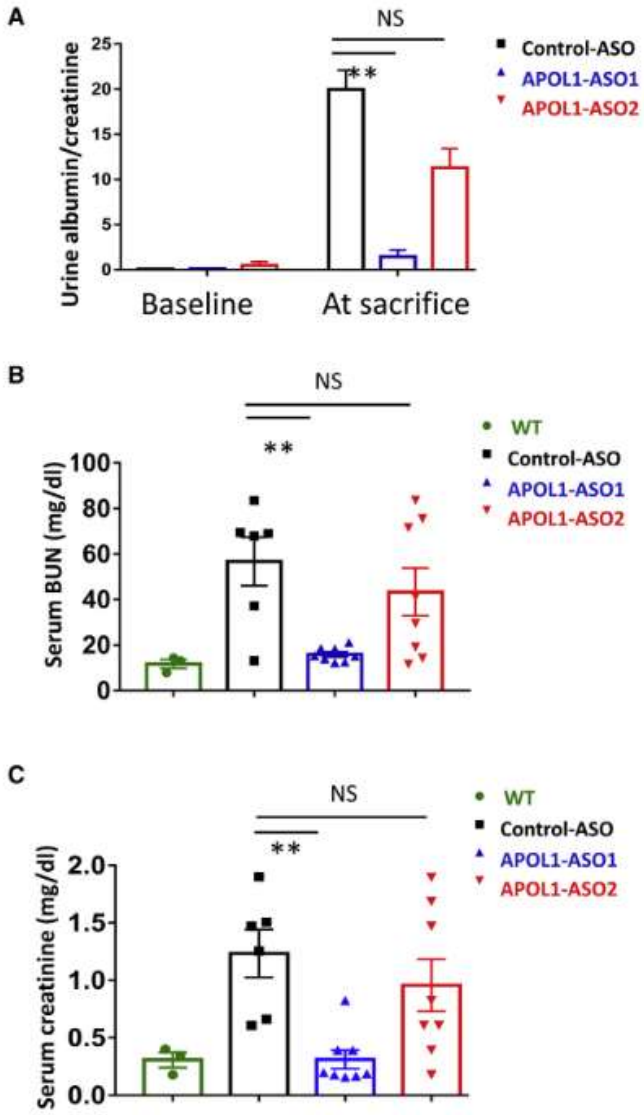
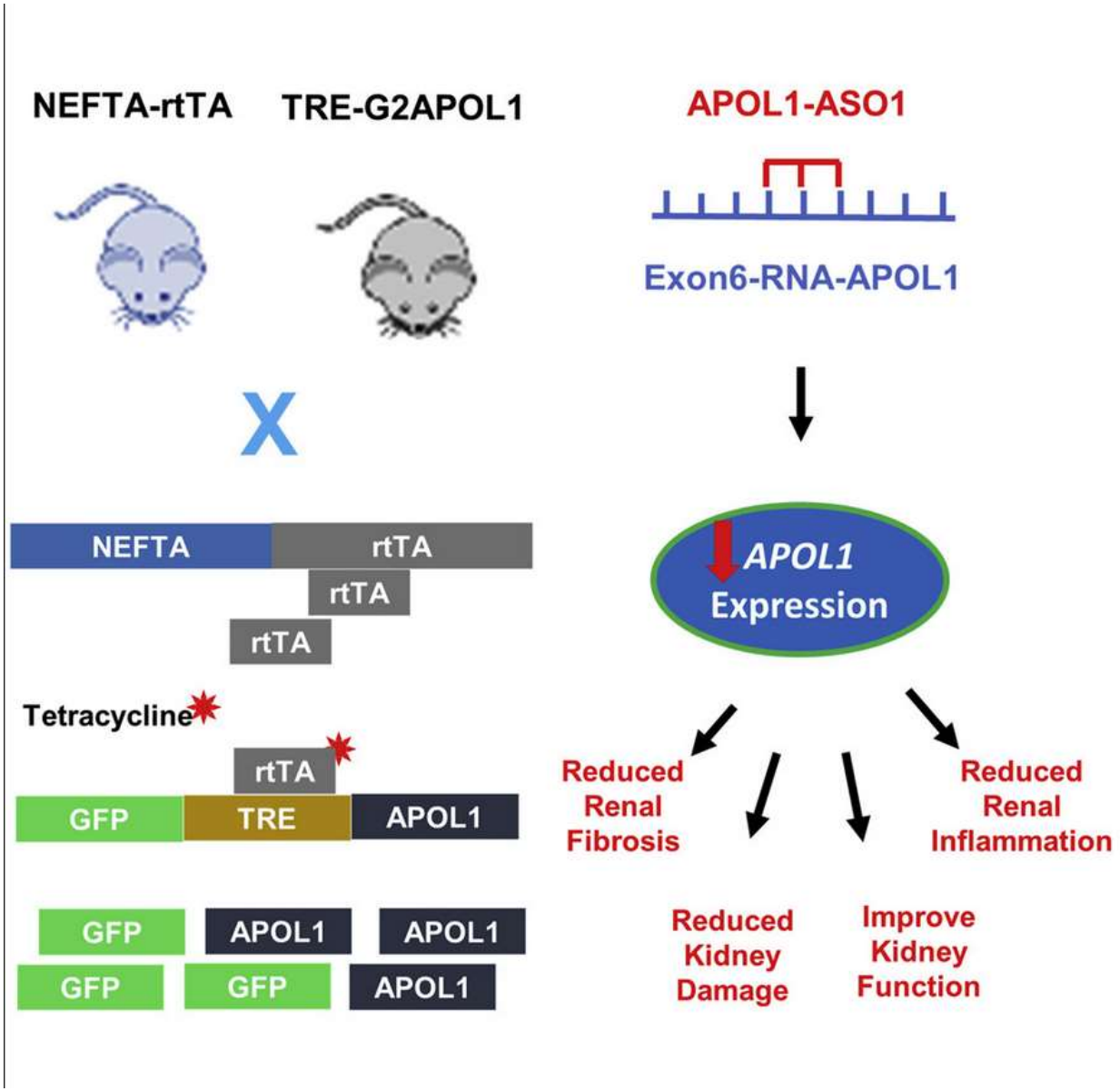


Figure 2. APOL1 ASO1 improves kidney function parameters in *NEFTA/G2APOL1* transgenic mice


NEFTA-rtTA
TRE-G2APOL1
X
NEFTA
rtTA
rtTA
rtTA
Tetracycline
rtTA
GFP
TRE
APOL1
GFP
APOL1
APOL1
GFP
GFP
APOL1
APOL1-ASO1
Exon6-RNA-APOL1
APOL1
Expression
Reduced
Renal
Fibrosis
Reduced
Kidney
Damage
Improve
Kidney
Function
Reduced
Renal
Inflammation

Abstract citation ID: gfae069.695

ERA 2024

#1003

Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple ascending doses of AZD2373, an antisense oligonucleotide targeting APOL1

Peter J. Greasley[1], Nikhil Agrawal[2], Magnus Althage[3], Jose Sanchez[4], Sarah Kirk[5], Erlend Johannessen Egeland[6], Magnus Åstrand[6], Helena Westergren[7], James Sherwood[8], Michael Mccarthy[9], Uptal Patel[2] and Iain Macphee[10]

-Phase 1, randomized, single-blind, placebo-controlled study (NCT05351047) in healthy male volunteers of West African ancestry

-18 participants w/ 1 or 2 copies of G1/G2
-Low, medium and high dose cohorts with 8 participants
- 6 weekly SC injections of AZD2373 (n = 6) or placebo (n = 2) followed up for 9-weeks post-last dose.

Plasma ApoL1

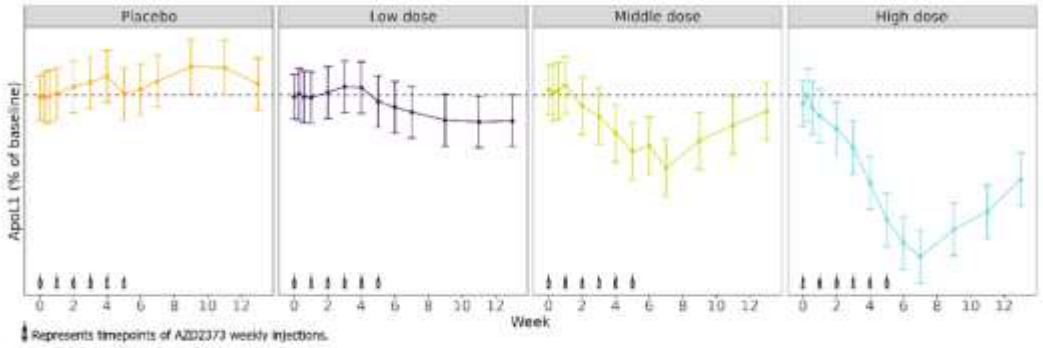
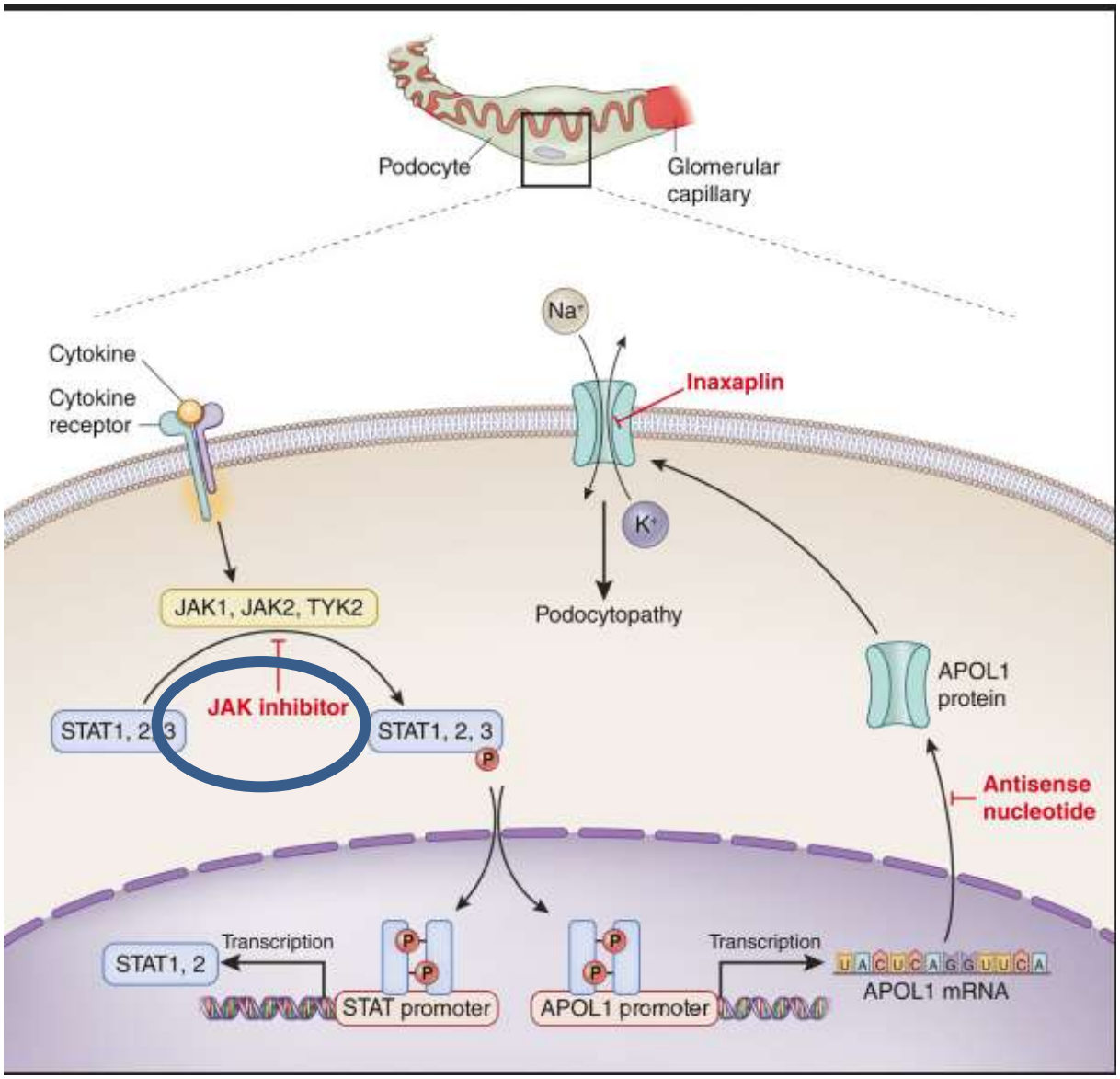


Figure: Geometric mean (90% CI) percentage change from baseline in plasma APOL1 concentration (µg/mL) versus time by dose group.

- No major safety and tolerability concerns

Potential Therapies for Apol1 associated KD



RECRUITING

Janus Kinase-STAT Inhibition to Reduce APOL1 Associated Kidney Disease (JUSTICE)

ClinicalTrials.gov ID NCT05237388

Sponsor Duke University

Information provided by Duke University (Responsible Party)

Last Update Posted 2024-03-21

Inclusion Criteria:

- Adults 18-70 years
- High Risk APOL1 genotype (i.e., G1G1, G2G2, or G1G2)
- FSGS diagnosed by kidney biopsy or clinically diagnosed HTN-CKD
- UACR ≥300 mg/dL
- Estimated glomerular filtration rate (eGFR) ≥26 ml/min/1.73 m2 at screening
- Stable antihypertensive regimen for ≥ 1 month prior to enrolment

PEP: Percent change in albuminuria (UACR)

SEP:

Percent change in eGFR (for 6 months]

Percent change in urine CXCL 9-11

Number of adverse events as measured by patient report

Number of adverse events (hemoglobin less than 9.5g/dL)

Genetic Testing for *APOL1*

Who should be tested?

- FSGS/SRNS
- ESKD of unknown etiology in patients <50 years + proteinuria
- “Hypertensive “ CKD
- HIV/COVID-associated nephropathy?
- Lupus nephritis with collapsing nephropathy/CKD?
- Sickle cell disease with proteinuria/CKD?

Advantages of *APOL1* genotyping

- *APOL1* testing may help a clinician understand the etiology of a patient’s kidney disease
- Institute preventive measures for the progression of kidney disease
- Predict kidney function, course of treatment, and disease progression
- May be informative in patients with a familial history of CKD
- Identify patients for enrollment in clinical trials

1. KDIGO Glomerular Diseases Clinical Practice Guideline 2021. ; 2. Knoers N, et al. *Nephrol Dial Transplant*. 2022;37:239-254; 3. Friedman DJ and Pollak MR. *Clin J Am Soc Nephrol*. 2021;16:294-303; 4. Young BA, et al. *Semin Nephrol.* 2017;37:552-557; 5. Freedman BI, et al. *J Am Soc Nephrol.* 2021;32:1765-1778.

Genetic Testing for *APOL1*

Who should be tested?

- FSGS/SRNS
- ESKD of unknown etiology in patients <50 years + proteinuria
- “Hypertensive “ CKD
- HIV/COVID-associated nephropathy?
- Lupus nephritis with collapsing nephropathy/CKD?
- Sickle cell disease with proteinuria/CKD?

Advantages of *APOL1* genotyping

- *APOL1* testing may help a clinician understand the etiology of a patient’s kidney disease
- Institute preventive measures for the progression of kidney disease
- Predict kidney function, course of treatment, and disease progression
- May be informative in patients with a familial history of CKD
- Identify patients for enrollment in clinical trials

Living kidney donors ?

Decision related to kidney transplant

1. KDIGO Glomerular Diseases Clinical Practice Guideline 2021. ; 2. Knoers N, et al. *Nephrol Dial Transplant*. 2022;37:239-254; 3. Friedman DJ and Pollak MR. *Clin J Am Soc Nephrol*. 2021;16:294-303; 4. Young BA, et al. *Semin Nephrol.* 2017;37:552-557; 5. Freedman BI, et al. *J Am Soc Nephrol.* 2021;32:1765-1778.